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EXHIBIT #22	Obama Crisis Plan 2011

COMPLAINT

EXHIBIT #1

Boone County Resolution

Boone County Resolution:

In addition to all other powers and duties now conferred by law upon county commissions, the Boone County Commission is "authorized to enact ordinances, issue orders and take other appropriate and necessary actions for the elimination of hazards to public health and safety and to abate or cause to be abated anything which the commission determines to be a public nuisance." W. Va. Code § 7-1-3kk [2002].

"A ***public nuisance*** is an act or condition that unlawfully operates to hurt or inconvenience an indefinite number of persons. The distinction between a public nuisance and a private nuisance is that the former affects the general public, and the latter injures one person or a limited number of persons only. Ordinarily, a suit to abate a public nuisance cannot be maintained by an individual in his private capacity, as it is the duty of the proper public officials to vindicate the rights of the public." *Sharon Steel Corp. v. City of Fairmont*, 175 W. Va. 479, 483, 334 S.E.2d 616, 620 (1985).

Between 2007 and 2012, more than 14 million doses of prescription pain pills were sold in Boone County which has a 2010 census population of 24,629. The dumping of millions of pain pills into our community has spawned a public health and safety hazard to the residents of Boone County, devastated our families, hurt our economy, wasted our public resources and created a generation of narcotic dependence.

Those in the chain of distribution have wrongfully abused the privilege of providing medication to our residents and must be held accountable. It is the duty of the Boone County Commission to vindicate the rights of the residents of Boone County and take action to abate this public nuisance.

Therefore, **BE IT RESOLVED** that the Boone County Commission hereby declares that the wrongful distribution of prescription pain pills, including hydrocodone and oxycodone, has created a public nuisance to the people of Boone County.

FURTHERMORE, the Boone County Commission hereby retains the law firm of GREENE, KETCHUM, FARRELL, BAILEY & TWEEL as counsel, on a contingent fee basis, to hold accountable those in the chain of distribution who caused this public nuisance and abate the same by seeking all civil remedies which may be afforded under West Virginia law. Paul T. Farrell, Jr., Esq. shall serve as lead counsel.

The adoption of the foregoing motion, having been made by Mickey Brown, Commissioner, seconded by Craig Bratcher, Commissioner, the vote thereon was as follows:

Eddie Hendricks, President.....AYE

Mickey Brown, Commissioner.....AYE

Craig Bratcher, Commissioner.....AYE

Whereupon, Eddie Hendricks, Commission President, declared said motion duly adopted; and it is therefore ADJUDGED and ORDERED that said motion be, and the same is hereby adopted.

Eddie Hendricks, President

Mickey Brown, Commissioner

Craig Bratcher, Commissioner

COMPLAINT

EXHIBIT #2

DEA letter September 27, 2006

U.S. DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

www.dea.gov Washington, D.C. 20537

CARDINAL HEALTH
2045 INTERSTATE DRIVE
LAKELAND, FL 33805-0000

September 27, 2006

In reference to registration
RC0182080

Dear Sir or Madam

This letter is being sent to every commercial entity in the United States registered with the Drug Enforcement Administration (DEA) to distribute controlled substances. The purpose of this letter is to reiterate the responsibilities of controlled substance distributors in view of the prescription drug abuse problem our nation currently faces.

Background

As each of you is undoubtedly aware, the abuse (nonmedical use) of controlled prescription drugs is a serious and growing health problem in this country.[1] DEA has an obligation to combat this problem as one of the agency's core functions is to prevent the diversion of controlled substances into illicit channels. Congress assigned DEA to carry out this function through enforcement of the Controlled Substances Act (CSA) and DEA regulations that implement the Act.

The CSA was designed by Congress to combat diversion by providing for a closed system of drug distribution, in which all legitimate handlers of controlled substances must obtain a DEA registration and, as a condition of maintaining such registration, must take reasonable steps to ensure that their registration is not being utilized as a source of diversion. Distributors are, of course, one of the key components of the distribution chain. If the closed system is to function properly as Congress envisioned, distributors must be vigilant in deciding whether a prospective customer can be trusted to deliver controlled substances only for lawful purposes. This responsibility is critical, as Congress has expressly declared that the illegal distribution of controlled substances has a substantial and detrimental effect on the health and general welfare of the American people.[2]

The Statutory Scheme and Legal Duties of Distributors as DEA Registrants

Although most distributors are already well aware of the following legal principles, they are reiterated here as additional background for this discussion.

The CSA uses the concept of registration as the primary means by which manufacturers, distributors, and practitioners are given legal authority to handle controlled substances. Registration also serves as the primary incentive for compliance with the regulatory requirements of the CSA and DEA regulations, as Congress gave DEA authority under the Act to revoke and suspend registrations for failure to comply with these requirements. (Depending on the circumstances, failure to comply with the regulatory requirements might also provide the basis for criminal or civil action under the CSA.)

[1] See National Institute on Drug Abuse Research Report, Prescription Drug Abuse and Addiction (revised August 2005) available at www.drugabuse.gov/PDF/RRPrescription.pdf.

[2] 21 U.S.C. 801(2).

ATTACHMENT 1

Before taking an action to revoke a registration, DEA must serve the registrant an order to show cause, which advises the registrant of its right to an administrative hearing before the agency (21 U.S.C 824(c)). The CSA also gives DEA discretionary authority to suspend any registration simultaneously with the initiation of revocation proceedings in cases where the agency finds there is an imminent danger to the public health and safety (21 U.S.C. 824(d)).

DEA recognizes that the overwhelming majority of registered distributors act lawfully and take appropriate measures to prevent diversion. Moreover, all registrants - manufacturers, distributors, pharmacies, and practitioners - share responsibility for maintaining appropriate safeguards against diversion. Nonetheless, given the extent of prescription drug abuse in the United States, along with the dangerous and potentially lethal consequences of such abuse, even just one distributor that uses its DEA registration to facilitate diversion can cause enormous harm. Accordingly, DEA will use its authority to revoke and suspend registrations in appropriate cases.

The statutory factors DEA must consider in deciding whether to revoke a distributor's registration are set forth in 21 U.S.C. 823(e). Listed first among these factors is the duty of distributors to maintain effective controls against diversion of controlled substances into other than legitimate medical, scientific, and industrial channels. In addition, distributors must comply with applicable state and local law. Congress also gave DEA authority under this provision to revoke a registration based on the distributor's past experience in the distribution of controlled substances and based on "such other factors as may be relevant to and consistent with the public health and safety."

The DEA regulations require all distributors to report suspicious orders of controlled substances. Specifically, the regulations state in 21 C.F.R. 1301.74(b):

> The registrant shall design and operate a system to disclose to the registrant suspicious orders of controlled substances. The registrant shall inform the Field Division Office of the Administration in his area of suspicious orders when discovered by the registrant. Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.

It bears emphasis that the foregoing reporting requirement is in addition to, and not in lieu of, the general requirement under 21 U.S.C. 823(e) that a distributor maintain effective controls against diversion.

Thus, in addition to reporting all suspicious orders, a distributor has a statutory responsibility to exercise due diligence to avoid filling suspicious orders that might be diverted into other than legitimate medical, scientific, and industrial channels. Failure to exercise such due diligence could, as circumstances warrant, provide a statutory basis for revocation or suspension of a distributor's registration.

In a similar vein, given the requirement under section 823(e) that a distributor maintain effective controls against diversion, a distributor may not simply rely on the fact that the person placing the suspicious order is a DEA registrant and turn a blind eye to the suspicious circumstances. Again, to maintain effective controls against diversion as section 823(e) requires, the distributor should exercise due care in confirming the legitimacy of all orders prior to filling.

In addition, distributors are required to file reports of distributions of certain controlled substances to the DEA ARCOS Unit, in the time and manner specified in the regulations (21 C.F.R. 1304.33). The failure to file ARCOS reports in a complete and timely manner is a potential statutory basis for revocation under section 823(e). Depending on the circumstances, the failure to keep or furnish required records might also be the basis for civil fines or criminal penalties under the CSA, as provided in 21 U.S.C. 842.

Circumstances That Might Be Indicative of Diversion

DEA investigations have revealed that certain pharmacies engaged in dispensing controlled substances for other than a legitimate medical purpose often display one or more of the following characteristics in their pattern of ordering controlled substances:

1. Ordering excessive quantities of a limited variety of controlled substances (e.g., ordering only phentermine, hydrocodone, and alprazolam) while ordering few, if any other drugs

2. Ordering a limited variety of controlled substances in quantities disproportionate to the quantity of non-controlled medications ordered

3. Ordering excessive quantities of a limited variety of controlled substances in combination with excessive quantities of lifestyle drugs

4. Ordering the same controlled substance from multiple distributors

A distributor seeking to determine whether a suspicious order is indicative of diversion of controlled substances to other than legitimate medical channels may wish to inquire with the ordering pharmacy about the following:

1. What percentage of the pharmacy's business does dispensing controlled substances constitute?

2. Is the pharmacy complying with the laws of every state in which it is dispensing controlled substances?

3. Is the pharmacy soliciting buyers of controlled substances via the Internet or is the pharmacy associated with an Internet site that solicits orders for controlled substances?

4. Does the pharmacy, or Internet site affiliated with the pharmacy, offer to facilitate the acquisition of a prescription for a controlled substance from a practitioner with whom the buyer has no pre-existing relationship?

5. Does the pharmacy fill prescriptions issued by practitioners based solely on an on-line questionnaire without a medical examination or bona-fide doctor-patient relationship?

6. Are the prescribing practitioners licensed to practice medicine in the jurisdictions to which the controlled substances are being shipped, if such a license is required by state law?

7. Are one or more practitioners writing a disproportionate share of the prescriptions for controlled substances being filled by the pharmacy?

8. Does the pharmacy offer to sell controlled substances without a prescription?

9. Does the pharmacy charge reasonable prices for controlled substances?

10. Does the pharmacy accept insurance payment for purchases of controlled substances made via the Internet?

These questions are not all-inclusive; nor will the answer to any of these questions necessarily determine whether a suspicious order is indicative of diversion to other than legitimate medical channels. Distributors should consider the totality of the circumstances when evaluating an order for controlled substances, just as DEA will do when determining whether the filling of an order is consistent with the public interest within the meaning of 21 U.S.C. 823(e).

We look forward to continuing to work in cooperation with distributors toward our mutual goal of preventing the diversion of pharmaceutical controlled substances.

Sincerely,

Joseph T. Rannazzisi
Deputy Assistant Administrator
Office of Diversion Control

COMPLAINT

EXHIBIT #3

DEA letter December 27, 2007

U.S. DEPARTMENT OF JUSTICE

DRUG ENFORCEMENT ADMINISTRATION

www.dea.gov Washington, D C 20537

CARDINAL HEALTH
2045 INTERSTATE DRIVE
LAKELAND FL 33805-0000

December 27, 2007

In reference to registration
RC0182080

Dear Registrant.

This letter is being sent to every entity in the United States registered with the Drug Enforcement Administration (DEA) to manufacture or distribute controlled substances. The purpose of this letter is to reiterate the responsibilities of controlled substance manufacturers and distributors to inform DEA of suspicious orders in accordance with 21 CFR 1301.74(b).

In addition to, and not in lieu of, the general requirement under 21 USC 823, that manufacturers and distributors maintain effective controls against diversion, DEA regulations require all manufacturers and distributors to report suspicious orders of controlled substances. Title 21 CFR 1301.74(b), specifically requires that a registrant "design and operate a system to disclose to the registrant suspicious orders of controlled substances." The regulation clearly indicates that it is the sole responsibility of the registrant to design and operate such a system. Accordingly, DEA does not approve or otherwise endorse any specific system for reporting suspicious orders. Past communications with DEA, whether implicit or explicit, that could be construed as approval of a particular system for reporting suspicious orders, should no longer be taken to mean that DEA approves a specific system.

The regulation also requires that the registrant inform the local DEA Division Office of suspicious orders when discovered by the registrant. Filing a monthly report of completed transactions (e.g., "excessive purchase report" or "high unit purchase") does not meet the regulatory requirement to report suspicious orders. Registrants are reminded that their responsibility does not end merely with the filing of a suspicious order report. Registrants must perform adequate due diligence and conduct an independent analysis of suspicious orders prior to completing a sale to determine whether the controlled substances are likely to be diverted from legitimate channels. Reporting an order as suspicious will not absolve the registrant of responsibility if the registrant knew, or should have known, that the controlled substances were being diverted.

The regulation specifically states that suspicious orders include orders of an unusual size, orders deviating substantially from a normal pattern, and orders of an unusual frequency. These criteria are disjunctive and are not all inclusive. For example, if an order deviates substantially from a normal pattern, the size of the order does not matter and the order should be reported as suspicious. Likewise, a registrant need not wait for a "normal pattern" to develop over time before determining whether a particular order is suspicious. The size of an order alone, whether or not it deviates from a normal pattern, is enough to trigger the registrant's responsibility to report the order as suspicious. The determination of whether an order is suspicious depends not only on the ordering patterns of the particular customer, but also on the patterns of the registrant's customer base and the patterns throughout the relevant segment of the regulated industry.

ATTACHMENT 2

Registrants that rely on rigid formulas to define whether an order is suspicious may be failing to detect suspicious orders For example, a system that identifies orders as suspicious only if the total amount of a controlled substance ordered during one month exceeds the amount ordered the previous month by a certain percentage or more is insufficient This system fails to identify orders placed by a pharmacy if the pharmacy placed unusually large orders from the beginning of its relationship with the distributor Also, this system would not identify orders as suspicious if the order were solely for one highly abused controlled substance if the orders never grew substantially. Nevertheless, ordering one highly abused controlled substance and little or nothing else deviates from the normal pattern of what pharmacies generally order.

When reporting an order as suspicious, registrants must be clear in their communications with DEA that the registrant is actually characterizing an order as suspicious. Daily, weekly, or monthly reports submitted by a registrant indicating "excessive purchases" do not comply with the requirement to report suspicious orders, even if the registrant calls such reports "suspicious order reports."

Lastly, registrants that routinely report suspicious orders, yet fill these orders without first determining that order is not being diverted into other than legitimate medical, scientific, and industrial channels, may be failing to maintain effective controls against diversion. Failure to maintain effective controls against diversion is inconsistent with the public interest as that term is used in 21 USC 823 and 824, and may result in the revocation of the registrant's DEA Certificate of Registration.

For additional information regarding your obligation to report suspicious orders pursuant to 21 CFR 1301.74(b), I refer you to the recent final order issued by the Deputy Administrator, DEA, in the matter of Southwood Pharmaceuticals Inc., 72 FR 36487 (2007). In addition to discussing the obligation to report suspicious orders when discovered by the registrant, and some criteria to use when determining whether an order is suspicious, the final order also specifically discusses your obligation to maintain effective controls against the diversion of controlled substances.

Sincerely,

Joseph T. Rannazzisi
Deputy Assistant Administrator
Office of Diversion Control

COMPLAINT

EXHIBIT #4

Declaration of Joseph Rannazzisi

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

CARDINAL HEALTH INC., Plaintiff, v. ERIC HOLDER, JR., ATTORNEY GENERAL, et al., Defendant.	Civil Action No. 1:12-cv-185 (RBW)

DECLARATION OF JOSEPH RANNAZZISI

I, Joseph Rannazzisi, pursuant to 28 U.S.C. § 1746, declare and state as follows:

1. I am currently the Deputy Assistant Administrator for DEA's Office of Diversion Control. In that capacity I coordinate the day-to-day operations of the Diversion Control Program; brief representatives from the pharmaceutical industry, members of Congress, executive staff at the Department of Justice and the Office of National Drug Control Policy, as well as the general public on the national epidemic of prescription drug abuse and the diversion of controlled substance pharmaceuticals.

2. I am a Special Agent of the United States Department of Justice, Drug Enforcement Administration (DEA) and have been employed by the DEA since 1986. Additionally, I have a Bachelor of Science Degree in Pharmacy and am a licensed pharmacist. I also hold a Juris Doctorate from the Detroit College of Law at Michigan State University.

3. The matters contained in this declaration are based upon my personal knowledge, training, and experience, and upon conclusions and determinations reached by me. I participated in the decision-making process that led to the issuance of an Immediate Suspension Order against Plaintiff Cardinal Lakeland. The contents of the declaration, including history, facts, conclusions, and determinations, formed the basis for the Administrator's decision to issue the ISO.

Regulatory Scheme

4. The Food and Drug Administration generally regulates pharmaceutical drugs. Congress, however, recognized the need for greater scrutiny over controlled substances, due to their potential for abuse and danger to public health and safety. As such, it established a separate framework under the Controlled Substances Act (CSA), 21 U.S.C. § 801 *et seq.*, and implementing regulations, that creates a closed system of distribution for all controlled substances and listed chemicals. *See* H.R. Rep. No. 91-1444, 1970 U.S.C.C.A.N. at 4566

5. Congress therefore established a comprehensive regulatory scheme in which controlled substances are placed in one of five "Schedules" depending on their potential for abuse, the extent to which they may lead to psychological or physical dependence, and whether they have a currently accepted medical use in treatment in the United States. *See* 21 U.S.C. § 812(b). Controlled substances in "Schedule I" have a "high potential for abuse," "no currently accepted medical use in treatment in the United States," and a "lack of accepted safety for use under medical supervision." 21 U.S.C. § 812(b)(1)(A)-(C). Controlled substances in Schedule II do have "a currently accepted medical use in treatment in the United States or a currently

accepted medical use with severe restrictions, but still have "a high potential for abuse." "Abuse of the drug or other substances may lead to severe psychological or physical dependence." 21 U.S.C. § 812(b)(2)(A)-(C).

6. The CSA gives the Drug Enforcement Administration broad authority to prevent the diversion of pharmaceutical drugs for illicit use. *See* 21 U.S.C. §§ 824(d), 871(a); 21 C.F.R. §§ 1316.65(c) and 1316.67; 28 C.F.R. § 0.104, Appendix to Subpart R, Sec. 7(a).

7. As part of that authority, the DEA Office of Diversion Control regulates every link in the prescription-drug supply chain and is responsible for regulating more than 1.4 million DEA registrants. Every person who manufactures, distributes, dispenses, imports, or exports any controlled substance or who proposes to engage in the manufacture, distribution, dispensing, importation or exportation of any controlled substance shall obtain a registration with DEA. 21 C.F.R. § 1301.11. It is the responsibility of the Office of Diversion Control to ensure that these registrants adhere to all aspects of the CSA and implementing regulations and to take action against them when they are out of compliance.

8. The closed system of the CSA is specifically designed with checks and balances between registrants to ensure that controlled substances are not diverted from this closed system.

9. Specifically, with respect to distributors, registrants are required to "maintain … effective control against diversion of particular controlled substances into other than legitimate medical, scientific, and industrial channels…." 21 U.S.C. § 823(b)(1) (detailing the obligation of distributors of controlled substances in Schedule I or II).

See also 21 U.S.C. § 823(e)(1) (detailing the obligation of distributors of controlled substances in Schedules III, IV, or V, to include "maintenance of effective controls against diversion of particular controlled substances into other than legitimate medical, scientific, and industrial channels"). With respect to distributors, "The registrant shall design and operate a system to disclose to the registrant suspicious orders of controlled substances.... Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency." 21 C.F.R. § 1301.74(b).

10. When registrants at every level—practitioners, pharmacies and distributors—fail to fulfill their obligations, these necessary checks and balances collapse. Because distributors handle such large volumes of controlled substances, and are the first major line of defense in the movement of legal pharmaceutical controlled substances and List I Chemicals from legitimate channels into the illicit market, it is incumbent on distributors to maintain effective controls to prevent diversion of controlled substances. Should a distributor deviate from these checks and balances, the closed system created by the CSA collapses.

11. When a distributor maintains multiple locations for distributing and selling controlled substances, it generally must obtain a separate registration for each location. *See* 21 U.S.C. § 822(e); 21 C.F.R. § 1301.12(a). This is necessary so that the DEA can identify and inspect all locations from which controlled substances are distributed.

12. When a distributor is not adhering to its legal obligations, the DEA has authority to revoke or suspend its registration. *See* 21 U.S.C. § 823(b) and (e) (describing that issuance of a distributor's registration must be consistent with the public interest, as

determined by the following five factors: (1) maintenance of effective control against diversion of particular controlled substances into other than legitimate medical, scientific, and industrial channels; (2) compliance with applicable State and local law; (3) prior conviction record of applicant under Federal or State laws relating to the manufacture, distribution, or dispensing of such substances; (4) past experience in the distribution of controlled substances; and (5) such other factors as may be consistent with the public health and safety). Ordinarily, DEA must hold a hearing prior to revocation or suspension of an entity's registration. But when the DEA has reason to believe that a registrant's continued operation would pose "an imminent danger to the public health or safety," DEA has discretion to suspend that party's registration immediately, prior to an administrative hearing. 21 U.S.C. § 824(d). DEA must provide the basis for its suspension in an Order to Show Cause. 21 C.F.R. § 1309.44(a). A § 824(d) suspension remains in effect until the DEA issues a final order, unless the suspension is withdrawn by the Attorney General or dissolved by a court of competent jurisdiction. 21 U.S.C. § 824(d).

The Rampant Problem of Controlled Substance Diversion for Illicit Use

13. Prescription drug abuse occurs in the United States at an alarming rate. The 2010 National Survey on Drug Use and Health reveals that approximately 7 million Americans abuse controlled substance pharmaceuticals for non-medical purposes. *See* 2010 National Survey on Drug Use and Health Survey, (2010 Survey) available at http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.pdf. Second only

to marijuana, controlled substance prescription drugs are abused by more people than cocaine, heroin, hallucinogens and inhalants combined.

14. Of all prescription drugs, narcotic pain relievers such as oxycodone, hydrocodone, and oxymorphone are abused most frequently. Each year, roughly 5.1 million people abuse narcotic pain relievers in the United States. Oxycodone is a Schedule II controlled substance.

15. Over the past several years, DEA has seen two major schemes used to divert powerful and addictive controlled substance pharmaceuticals. First, between 2005 and 2009, hydrocodone, a Schedule III controlled substance, was illegally diverted through rogue Internet pharmacy schemes. Florida was the epicenter for many of the illegal operations whereby tens of millions of dosage units of hydrocodone were diverted to locations across the United States. For reference, a dosage unit is most commonly applied to a tablet. It is the main ingredient, expressed in milligrams or milliliters (liquids), in combination with other ingredients, binders and fillers. Congress reacted to the plethora of rogue Internet pharmacies with the passage of the Ryan Haight Online Pharmacy Consumer Protection Act that took effect in April 2009. This action along with intensified law enforcement actions virtually eliminated domestic-based rogue Internet pharmacies.

16. Second, beginning in late 2008 and continuing to the present, there has been a significant rise in the number of rogue pain clinics whose complicit doctors initially dispensed millions of dosage units of oxycodone, a Schedule II controlled substance, 21 C.F.R. § 1308.12(b)(1)(xiii), more potent than the hydrocodone that was previously dispensed through the rogue Internet operations. Again, Florida was and

remains the epicenter for these illegal pain clinics. DEA, State and local law enforcement investigations reveal that thousands of drug seekers flock to these Florida-based pain clinics to obtain their supply of oxycodone, and other controlled substances such as alprazolam, which is in turn illegally redistributed in states along the entire east coast and Midwest.

17. Florida has attempted to address this problem through a patchwork of legislation. Some of the more current state legislation has placed a restriction on a physician's ability to dispense oxycodone from the clinic. The illicit pain clinics responded by issuing prescriptions for oxycodone rather than dispensing directly to the drug seeker. DEA and other law enforcement agencies saw an immediate and significant increase in the volume of oxycodone dispensed from various pharmacies across the state. DEA registered pharmacies are generally supplied by DEA registered wholesale distributors such as Cardinal Lakeland.

18. The illicit pain clinics, the pharmacies that fill their scripts, and the wholesale distributors who supply pharmacies without appropriate due diligence (including Cardinal Health's Lakeland, Florida, distribution center), have caused, and continue to cause, millions of dosage units of oxycodone and other controlled substances to be diverted and pose an imminent threat to the public health and safety. According to the Florida Medical Examiner's Office, they have seen a 345.9% increase in the number of overdose deaths associated with oxycodone between 2005 and 2010. For 2010, their data showed that approximately 4,091 persons died in Florida alone from an overdose caused by just five drugs: methadone, oxycodone, hydrocodone,

benzodiazepines, or morphine. This is an average of 11.2 persons dying in the state of Florida every day from just these five drugs alone.

19. Furthermore, the abuse of prescription drugs is not isolated to just one drug. Abusers and addicts routinely abuse prescription drugs in combination with one another to enhance the effects. This activity significantly increases the risk of potential harm to the individual. This combination is often referred to as the "trinity" or "holy trinity," hydrocodone or oxycodone used in combination with alprazolam (a benzodiazepine) and carisoprodol. According to the Florida Medical Examiner's Office, they have seen a 127% increase in the number of deaths associated with benzodiazepines in the State of Florida between 2005 and 2010.

20. From approximately February 2009 through June 2010, monthly oxycodone sales to Florida practitioners steadily increased and well-surpassed the monthly oxycodone sales in the remaining states. In June 2010, DEA took action on wholesale distributors supplying Florida practitioners at rogue pain clinics. Once DEA took action on wholesale distributors, monthly oxycodone sales to practitioners in Florida substantially decreased. Despite this decrease in monthly oxycodone sales beginning in June 2010, Cardinal's sales to its top four Florida retail pharmacy customers, on average, continued to increase. Attachments 1 and 2.

21. During the same time period, Florida has tried to rein in prescription-drug abuse by enacting laws that limit Florida physicians' ability to dispense controlled substances. Until 2010, FLA. STAT. § 465.0276 allowed a practitioner to dispense drugs in the usual course of professional practice so long as s/he was registered as such and paid a $100 fee. The practitioner was subject to the same record-keeping requirements and

periodic inspections as a pharmacy. In 2010, the Florida legislature amended FLA. STAT. § 465.0276 to prohibit a registered practitioner from dispensing more than a 72-hour supply of any controlled substance for any patient who paid for the medication with cash, check or credit card. The law became effective October 1, 2010. Finally, in 2011, the Florida legislature amended the statute a second time to prohibit a practitioner, except in very limited circumstances, from dispensing any controlled substances in Schedules II and III. The law became effective July 1, 2011.

22. On July 1, 2011, the State Health Officer and Surgeon General, Dr. Frank Farmer issued a statewide public health emergency declaration in response to the ongoing problem of prescription drug abuse and diversion in Florida, titled "State Surgeon General Declares Public Health Emergency Regarding Prescription Drug Abuse Epidemic." The press release noted that "In 2010, 98 of the top 100 doctors dispensing Oxycodone nationally were in Florida;" that "In 2010, 126 million Oxycodone pills were dispensed through the top 100 dispensing pharmacies in Florida;" "More Oxycodone is dispensed in the state of Florida than in the remaining states combined." Attachment 3.

23. The changes in the law have changed the way drug abusers obtain oxycodone. Rather than dispensing the drug directly to "patients," pain clinics and complicit doctors now write prescriptions for oxycodone. Drug abusers wanting their prescriptions filled must take their script to a retail pharmacy.

24. Following these changes in the law, law enforcement saw immediate and significant increases in the volume of oxycodone dispensed from retail pharmacies across the state of Florida. Retail pharmacies are generally supplied by a DEA-registered

wholesale distributor. One such distributor, Cardinal Lakeland, continued to distribute significant amounts of oxycodone to its top four retail pharmacy customers that well-exceeded the average distributions to their own Florida retail pharmacy customers following the changes in the law. Attachment 4.

25. The doctors and clinics that prescribe oxycodone inappropriately, the pharmacies that dispense their prescriptions, and the wholesale distributors who supply them have caused, and continue to cause, millions of dosage units of oxycodone to be diverted for unlawful use thereby creating an imminent threat to the public health and safety.

DEA Efforts to Stop Diversion of Prescription Drugs Through Education/Outreach to Distributors:

26. To inform distributors of their obligations under the CSA, the DEA periodically sends guidance letters to all registered distributors and periodically meets with registered distributors as part of its "Distributor Initiative Program." The Program was designed to cut off the source of supply to rogue operations by ensuring that registrants understand and comply with their requirements under the CSA and its accompanying regulations.

27. As stated above, wholesale distributors are required to design and operate a system that would detect suspicious orders and report those suspicious orders to DEA. Through DEA's Distributor Initiative Program, DEA has discussed with registrants, including Cardinal Health, the firm's due diligence responsibilities under the CSA, including: knowing one's customers, suspicious order monitoring programs, trends in controlled substance abuse, theft and diversion, a thorough review of the distributor's own sales of controlled substances data obtained through DEA Automation of

Reports and Consolidated Orders System (ARCOS), a review of previous civil, administrative and criminal cases against DEA registrants, and how DEA expects the distributor to assist in the fight against the abuse and diversion of legitimately manufactured controlled substances. During these briefings DEA has thoroughly explained the problems in Florida associated with pain clinics, the drugs of abuse, such as oxycodone, hydrocodone, and others used in combination by drug seekers, the cost of this abuse to society, and what the distributor should look for when visiting customers in Florida to determine the legitimacy of their orders. DEA thoroughly explains what red flags the distributor needs to look for when determining whether to ship controlled substances. During the briefing DEA further states they expect the distributor to be a good corporate citizen and abide by all the provisions in the CSA and work hand in hand with DEA in fighting the abuse and diversion of controlled substances.

28. DEA provided the distributor briefing to Cardinal Health on or about August 22, 2005.

29. In addition, on or about September 27, 2006, DEA sent a letter to Cardinal Lakeland detailing the distributors' responsibility to ensure that their products are not diverted for illicit use. The letter reminded distributors that they have "a statutory responsibility to exercise due diligence to avoid filling suspicious orders that might be diverted into [illegitimate] channels," and warned that "failure to exercise such due diligence could . . . provide a statutory basis for revocation or suspension of a distributors registration." Attachment 48

30. The September 2006 letter cautioned that "a distributor may not simply rely on the fact that the person placing the suspicious order is a DEA registrant and turn a blind eye to the suspicious circumstances." *Id.* "[M]aintain[ing] effective controls against diversion," the letter continued, requires that "the distributor . . . exercise due care in confirming the legitimacy of all orders prior to filing." *Id.*

31. The September 2006 letter also identified "circumstances that might be indicative of diversion," including customers ordering the same controlled substances from multiple distributors, suggested what distributors might ask to determine whether an order is suspicious, and encouraged distributors to "consider the totality of the circumstances when evaluating an order for controlled substances." *Id.* at 3-4.

32. Customers ordering the same controlled substances from multiple distributors may be indicative of diversion due to the customer ultimately acquiring large amounts of controlled substances through multiple sources. Distributors are unable to access other distributor's information regarding distributions due to the proprietary nature of the information. The customer having multiple sources of distribution may avoid scrutiny by maintaining several sources to obtain controlled substances.

33. The DEA sent a similar letter on or about December 27, 2007. The letter reminded all distributors of their obligation "to maintain effective controls against diversion," and emphasized that "it is the sole responsibility of the registrant to design and operate" a "system to disclose to the registrant suspicious orders of controlled substances." The December 2007 letter highlighted the definition of "suspicious order" in the regulations: Suspicious orders are "orders of unusual size, orders deviating substantially from a normal pattern, and orders of an unusual frequency."

The letter stressed that "[t]hese criteria are disjunctive and are not all inclusive." It explained that "[t]he size of an order alone, whether or not it deviates from a normal pattern is enough to trigger the registrant's responsibility to report the order as suspicious." Attachment 5.

34. The letter also noted that "[r]egistrants that rely on rigid formulas to define whether an order is suspicious may be failing to detect suspicious orders. For example, a system that identifies orders as suspicious only if the total amount of a controlled substance ordered during one month exceeds the amount ordered the previous month by a certain percentage or more is insufficient." *Id.*

35. Additionally, DEA has maintained open communications with Cardinal Health in its efforts to improve its anti-diversion controls at Lakeland and other Cardinal facilities. Since November 3, 2008, Barbara Boockholdt, Office of Diversion Control, Regulatory Section Chief, has received at least sixty-six (66) emails from Cardinal employees Michael Moné and Steve Reardon. Additionally, Ms. Boockholdt has sent at least twenty-seven (27) emails to Cardinal employees. Between February 4, 2009 and October 3, 2011, Cardinal and DEA have exchanged dozens of phone calls. Following a DEA site visit at Cardinal Health in Dublin, Ohio the week of January 26, 2009, DEA and Cardinal have held at least three (3) other face to face meetings with Ms. Boockholdt (November 20, 2009, March 15, 2011, and July 7, 2011).

36. In addition, DEA offers a variety of conferences which are open to DEA registrants, including distributors. In fact, records indicate that Cardinal sent three (3) representatives (including Mr. Moné and Mr. Reardon) to DEA's Pharmaceutical Industry Conference October 14-15, 2009. This conference promotes a closer

cooperation between the pharmaceutical industry and DEA. It provides an invaluable forum in which the pharmaceutical registrant community and DEA can engage in candid discussions concerning emerging diversion trends, interpretations of existing regulations and policies, issues requiring regulatory change, and clarifications of DEA policy.

37. DEA also provides presentations to and holds meeting with the industry trade group, Healthcare Distribution Management Association (HDMA) of which Cardinal Health is an active member. Between May 6, 2008 and December 31, 2011, DEA representatives gave presentations to and held meetings with HDMA in Maryland, the District of Columbia, Florida, and Virginia on eleven (11) occasions. And in November 2008, HDMA published a document entitled Industry Compliance Guidelines for use by its members which provided guidance on identifying and reporting suspicious orders and preventing diversion of controlled substances.

DEA's Collection of Proprietary Data and Monitoring:

38. To monitor the sale and distribution of controlled substances, manufacturers and distributors of controlled substances are required to report to DEA sale and distribution data for Schedule I and II materials; Schedule III narcotic and gamma-hydroxybutyric acid (GHB) materials; and selected Schedule III and IV psychotropic drugs (manufactures only). DEA collects large amounts of this data from its registrants using a computer system known as the Automation of Reports and Consolidated Orders System, or "ARCOS." Manufactures and distributors are not however required to report data on sale or distribution of all controlled substances to

the ARCOS system. All manufacturers and distributors registered with DEA must submit the required data to ARCOS on either a monthly or quarterly basis. ARCOS software enables the government to maintain current and historical data of selected controlled substance inventories and transactions from the point of manufacture to the point of sale, distribution, or other disposition, and finally, to the dispensing (consumption) level.

39. The data that DEA collects and maintains from these manufacturers and distributors is treated as privileged and confidential commercial information. Disclosure of company-specific information could cause competitive harm to the registrant from whom it was obtained and therefore is not permitted to be disclosed to the public. If a formal request for ARCOS information is made pursuant to the Freedom of Information Act (FOIA), the request is evaluated pursuant to the disclosure requirements under the law. *See* 5 U.S.C. 552(b)(4). While DEA has disclosed limited ARCOS data that is not proprietary in nature pursuant to both FOIA and non-FOIA requests as required by law, requests for proprietary information are routinely denied

40. The information that registrants submit to ARCOS is often proprietary, as it includes information about a registrant's sales and customer base. Because of the sensitive nature of the information, the DEA does not permit registrants to access other registrant's information in ARCOS. DEA does not disclose law enforcement sensitive information that may jeopardize on-going investigations and the release of information to a manufacturer or distributor regarding other registrants may jeopardize the due process rights of the registrant at issue. Because of each

registrant's right to due process under the CSA, the agency cannot tell a distributor or manufacturer that it cannot distribute controlled substances to another registrant. If, based on that information, a registrant could no longer find a supply of controlled substances, the agency has *de facto*, without due process, impermissibly denied it of its right to handle controlled substances.

Cardinal Health

41. Plaintiff Cardinal Health, Inc. is one of the nation's largest wholesale pharmaceutical drug distributors. *See* Compl. ¶ 20. Cardinal distributes pharmaceuticals and medical products for dispensing and retail sale. Oxycodone is one of the pharmaceutical drugs that Cardinal distributes.

42. According to DEA's records, there are twenty-five (25) Cardinal Health distributors registered with DEA in the United States, each possessing a separate DEA registration number. In addition to the Lakeland facility, at least two other distribution facilities, by Cardinal's own admissions, possess the requisite standards to meet Florida's pedigree requirements for the distribution of controlled substances into Florida.Giacomin Dec. at ¶ 7.

43. Cardinal Lakeland, located at 2045 Interstate Drive, Lakeland, Florida 33805 is registered with the DEA as a distributor in Schedules II, III, IV and V controlled substances under DEA Registration Number RC0182080. DEA Registration Number RC0182080 expires by its terms on August 31, 2012.

44. In total, 836 controlled substances distributors are registered with DEA, forty-nine (49) of which are registered in the state of Florida.

45. From January through December 2010, the top 25 distributors located in Florida distributed 597,215,253 dosage units of oxycodone to retail registrants in the state of Florida. For reference, a dosage unit is most commonly applied to a tablet. It is the main ingredient, expressed in milligrams or milliliters (liquids), in combination with other ingredients, binders and fillers. Cardinal Lakeland distributed 132,281,020 dosage units of the total oxycodone distributed, or approximately 22% of the total 2010 distributions by the top 25 Florida distributors.. Attachment 6.

46. From January through December 2011, the top 25 distributors located in Florida distributed 572,274,402 dosage units of oxycodone to retail registrants in the state of Florida. Cardinal Lakeland distributed 146,577,480 dosage units of the total oxycodone distributed, or approximately 25% of the total 2011 distributions by the top 25 Florida distributors. Attachment 7.

Cardinal's Prior Suspensions

47. DEA suspended operations at four Cardinal distribution facilities through a series of Immediate Suspension Orders issued between November 28, 2007 and January 30, 2008 based on the DEA's conclusion that they "failed to maintain effective controls against diversion." Attachments 8, 9, 10. Following Cardinal Lakeland's suspension, problems related to hydrocodone diversion in Florida decreased in 2007 and 2008. When the Cardinal Lakeland facility was previously suspended, Cardinal was able to fill and distribute orders to its Florida-based customers through its other distribution centers.

48. DEA also issued an Order to Show Cause to revoke the registration of the Stafford, Texas facility based on "failure to conduct appropriate due diligence." Attachment 11.

49. DEA immediately suspended Cardinal Lakeland based on its conclusion that, for approximately 2 years and two months, between August 2005 and October 2007, the facility "distributed over 8,000,000 dosage units of hydrocodone combination products to customers that it knew or should have known were diverting hydrocodone into other than legitimate medical, scientific and industrial channels." Attachment 9. The ISO noted that, although the average retail pharmacy in Florida distributes "less than 8,400 dosage units of hydrocodone per month," the ten retail pharmacies that Cardinal Lakeland supplied distributed considerably more. Monthly averages at those ten pharmacies ranged from 11,075 dosage units to a high of 287,025 dosage units. The ISO alleged that the "unusual size" of some of the orders, among other factors, should have prompted Cardinal to conclude that the orders "were 'suspicious' as that term is used in" the regulations. *Id.* Cardinal Lakeland and the other facilities ceased all distributions of controlled substances on the date they received the ISOs.

50. In addition to the four Cardinal distribution facilities that received ISOs, DEA also alleged that Cardinal "failed to maintain effective controls against the diversion of controlled substances" at three other facilities. *See* Attachment 12.

51. In total, the DEA had reason to believe that 7 of Cardinal's 27 distribution centers—roughly 25%--were not adhering to their responsibilities as registrants.

Cardinal's 2008 Memorandum of Agreement with DEA

52. Rather than continue administrative proceedings, Cardinal entered into an Administrative Memorandum of Agreement (MOA) with the DEA on September 30, 2008. Attachment 12.

53. The MOA settled DEA claims against Cardinal arising out of its investigation of the seven (7) distribution centers.

54. In the MOA, Cardinal agreed to "maintain a compliance program designed to detect and prevent diversion of controlled substances as required under the CSA and applicable DEA regulations." Attachment 12. Cardinal agreed, among other things, to have a "Cardinal employee trained to detect suspicious orders" review "orders that exceed established thresholds and criteria," and acknowledged that "the obligations undertaken in this subparagraph do not fulfill the totality of its obligations to maintain effective controls against the diversion of controlled substances." *Id.*

55. The MOA and corresponding settlement also required that Cardinal pay $34 million in civil penalties "in settlement of claims or potential claims for civil penalties made by the United States of America for failing to report suspicious orders of controlled substances." *Id.* at 5. Of that sum, Cardinal agreed to pay $16 million "for conduct alleged to have occurred within the Middle District of Florida," where Cardinal Lakeland is located. *Id.* The remainder was apportioned among the six other districts housing the Cardinal distribution centers at issue, in amounts ranging from $1-8 million. *Id.*

56. Prior to the DEA and Cardinal Health 2008 MOA, the largest civil monetary penalty paid by a DEA registrant pursuant to violations of the CSA was a $13.25 million civil

penalty assessed against McKesson in April 2008. Standing alone, the civil penalties assessed against the Lakeland distribution facility surpassed the existing record settlement in the McKesson case.

57. Cardinal Lakeland's ISO was lifted on October 2, 2008, the effective date of the MOA Attachment 12. In total, the Lakeland facility was suspended from distributing controlled substances for nearly ten months, between December 5, 2007, and October 2, 2008. During that time, two Cardinal distribution centers were also prohibited from distributing controlled substances because of their suspensions.

Notice to Cardinal Health of Diversion Problem

58. At the time of the initial investigation, Cardinal Lakeland's top four retail pharmacy customers were Holiday CVS, L.L.C., d/b/a CVS/Pharmacy # 00219 ("CVS 219"), located at 3798 Orlando, Sanford, Florida 32773; Gulf Coast Pharmacy, located at 3685 Doctor's Way, Ft. Myers, Florida 33912; Holiday CVS, L.L.C., d/b/a CVS/Pharmacy # 05195 ("CVS 5195"), located at 4369 West 1st Street, Sanford, Florida 32771; and Caremed Health Corporation, d/b/a Brooks Pharmacy ("Caremed"), located at 3501 Health Center Boulevard, Bonita Springs, Florida 34135.

59. DEA has communicated to Cardinal that it is required to conduct its own due diligence on its retail pharmacy chain customers. On July 28, 2009, DEA conducted a compliance review at Cardinal's distribution center located in Peabody, Massachusetts. DEA investigators asked the distribution center for due diligence files from a number of chain pharmacies, but Cardinal could not produce the requested due diligence files. Consequently, investigators spoke to Michael Moné, Quality and

Regulatory Affairs ("QRA") Vice President, Anti-Diversion & Supply Chain Services, Dublin, Ohio, via teleconference. During the teleconference, Mr. Moné stated that Cardinal Health communicates with the loss prevention individuals of chain pharmacies when an order is approaching or exceeding set thresholds and maintains e-mails of the communications. DEA Staff Coordinator Mike Arpaio communicated to Mr. Moné that due diligence investigations must be performed on all customers, chain pharmacies included, when it appears that suspicious high volume orders are requested of controlled substances and questionnaires should be sent to these chains. Mr. Moné in turn, stated that QRA is unable to look at chain pharmacy systems in order to identify problem areas when there is not an order of interest or their threshold is not exceeded. Staff Coordinator Mike Arpaio communicated to Cardinal that chain store due diligence reviews must not be treated any differently than independent retail pharmacy customers. Mike Arpaio specifically stated that Cardinal's due diligence responsibilities included conducting site visits at chain stores.

60. U.S. distributor registrants are subject to scheduled investigations by Diversion Investigators every three years. Since 2008, DEA has conducted nineteen (19) scheduled investigations which have resulted in two (2) Letters of Admonition, including further investigation of one of these facilities' due diligence program, an additional two investigations for failure to report suspicious orders, and one investigation for shipping to a registrant other than the registrant that ordered the controlled substances.

61. On July 7, 2011, DEA representatives from DEA Headquarters and the Seattle Field Division met with Cardinal Health at DEA Headquarters to discuss the firm's theft and loss reporting and conducting due diligence to maintain effective controls against diversion, with respect to Cardinal's Auburn, Washington distribution facility. DEA representatives further advised Cardinal with respect to their due diligence responsibilities, that Cardinal should examine their Florida customers, particularly, Cardinal's retail pharmacy chain customers. DEA did not indicate that its concern with Cardinal's Florida distributions was limited only to Cardinal's top few customers.

62. On August 23, 2011, DEA Headquarters representatives met with representatives of Mallinckrodt LLC, a manufacturer that sells oxycodone to Cardinal for distribution.

63. About three weeks after meeting with DEA, on September 16, 2011, Mallinckrodt sent a letter to forty-three (43) distributors, including Cardinal. The letter stated that it was no longer processing "charge backs" from distributor sales of Mallinckrodt's products to certain pharmacies, including Gulf Coast, which were identified in an included Attachment. "Charge backs" are credits that a pharmacy may receive from a manufacturer via a distributor in exchange for pharmacy dispensing information. Attachment 13. Mallinckrodt told its distributors that it "made our decision based on our recent site visits to these locations" and suggested that "if you have sold controlled substances to any of these pharmacies, you consider conducting an on-site audit as part of your [Suspicious Order Monitoring] program." *Id.*

64. Mallinckrodt met with Cardinal on September 30, 2011 to discuss levels of sales of Mallinckrodt's products to Cardinal in Florida. As part of the meeting, Mallinckrodt

gave Cardinal two lists – a list containing the top twenty (20) pharmacies by volume located in state and a second list based on the top twenty (20) pharmacies by volume located out of state, based on Cardinal's distributions of oxycodone thirty milligram and oxycodone fifteen milligram manufactured by Mallinckrodt. Attachment 14. Mallinckrodt advised Cardinal that they had suspended charge backs to those pharmacies. For Mallinckrodt to resume charge backs, Mallinckrodt stated to Cardinal that it must provide documentation of Suspicious Order Monitoring due diligence audits and conduct site visits within sixty (60) days for all forty (40) customers.

65. Based on the September 30, 2011 meeting with Mallinckrodt and Cardinal, Cardinal's own supplier gave notice to Cardinal of Cardinal's level of sales of thirty and fifteen milligram oxycodone, a controlled substance known to be abused in Florida.

DEA Investigation of Cardinal Lakeland and its Top Four Customers

66. On October 18, 2011, based on DEA's evaluation of ARCOS data regarding the top distributions of oxycodone in the United States, DEA executed Administrative Inspection Warrants ("AIWs") at Cardinal Lakeland's top four retail pharmacy Florida customers of oxycodone: CVS 219, Gulf Coast, CVS 5195, and Caremed.

67. Both Caremed and Gulf Coast voluntarily surrendered their DEA registration for cause. (Caremed surrendered when it received the AIW; Gulf Coast surrendered following the execution of a federal search warrant on November 5, 2011.)

68. On October 26, 2011, DEA executed an AIW at Cardinal Lakeland. The affidavit supporting the warrant stated that because "DEA is investigating Cardinal Health's top four customers to determine whether the pharmacies are dispensing controlled

substances outside the scope of their registration," "DEA also needs to determine whether Cardinal Health has failed to report suspicious orders to DEA." R. 3-12 at 7. DEA investigators gave Cardinal Lakeland a list of documents that needed to be provided to DEA.

69. On October 27, 2011, Cardinal sent DEA a letter asking the agency to "inform [Cardinal] of the identity of any Cardinal Health customer that the agency has determined is engaged in the diversion of controlled substances" and promising to "immediately cease distribution of controlled substances to any customer that DEA so identifies. R. 3-6 at 2.

70. On October 28, 2011, Cardinal Health provided 2 computer discs ("CDs") to DEA. The discs contained Cardinal's due diligence files, item audit reports, standard operating procedures, a Power Point presentation containing an overview of the facility, and a spreadsheet containing Cardinal's top fifty (50) customers from December 1, 2010 through October 26, 2011. On November 8, 2011, DEA issued an administrative subpoena to Cardinal Health for information regarding its sales of oxycodone (among other drugs) and its compliance mechanisms.

71. On November 18, 2011, Cardinal Health delivered a CD to DEA containing additional due diligence files, Excel spreadsheets of Cardinal's sales of oxycodone, alprazolam, and carisoprodol; and an Electronic Suspicious Order Monitoring spreadsheet.

72. In total, the information provided by Cardinal in response to the AIW, consisted of 1020.44 megabytes of information, which is a volume consistent with a distributor of Cardinal Lakeland's size.

73. To date, DEA has not received the compliance-related communications responsive to the November 8, 2011 administrative subpoena. Through counsel, Cardinal has communicated to DEA that it will not provide the requested information until the end of February 2012. Based on previous statements made by Cardinal employees relative to suspicious customers and their response, DEA believes that these documents will corroborate those statements and provide evidence critical to DEA's investigation of the Cardinal Lakeland facility.

Results of Cardinal Lakeland Investigation

Exponentially Increasing High-Volume Sales:

74. Based on its review of the documents Cardinal provided in response to the October 26, 2011 AIW and the November 8, 2011 administrative subpoena, the investigation at Cardinal Lakeland revealed a persistent failure to exercise due diligence to ensure that controlled substances were not being diverted. DEA concluded that over a period of approximately 3 years, November 2008 to December 2011, Cardinal's anti-diversion controls were inadequate to meet their due diligence responsibilities. This conclusion was based on the totality of several factors. Some of the most important factors were: (i) exceedingly large increasing volume of shipments of oxycodone to its largest Florida retail customers, which volumes were supported by inadequate documentation; (ii) a low number of suspicious orders reported; (iii) a low number of on-site visits to these top retailers and no site visits to retail chain pharmacy customers; and (iv) evidence that Cardinal's due diligence practices were inconsistent with both the 2008 MOA and Cardinal's own policies the purpose of which was to reduce diversion.

75. Between November 1, 2008 and December 31, 2011, Cardinal Lakeland sold over 12.9 million dosage units of oxycodone to its top four customers. From 2008 to 2009, Cardinal's oxycodone sales to its top four retail pharmacy customers increased approximately 803%. From 2009 to 2010, Cardinal's oxycodone sales increased approximately 162%. Attachment 15. Between 2009-2011, Cardinal's oxycodone sales to its top four retail pharmacies increased 241%. Attachment 2; see also Carter Decl. ¶¶ 7, 16, 25, 35

76. Compared to the average number of dosage units distributed monthly to Cardinal's other Florida retail pharmacies, the average monthly distribution at Cardinal's top four customers is staggering. Cardinal's other Florida retail pharmacies received, on average, 5,364 dosage units per month from October 1, 2008 through December 31, 2011 based on 66,286 pharmacies, which equates to 64,368 dosage units, annually. In contrast, CVS 5195 received approximately 58,223 dosage units per month from Cardinal; Caremed received 59,264 dosage units per month from Cardinal; Gulf Coast received 96,644 dosage units per month from Cardinal; and CVS 219 received 137,994 dosage units per month from Cardinal. Attachment 16. In total, Cardinal distributed approximately 3.225 million to each of its top four retail pharmacy customers from November 1, 2008 through December 31, 2011, based on a total distribution of 12.9 million dosage units from November 1, 2008 through December 31, 2011. Put another way, Cardinal's top four retailers received approximately 50 times the amount of oxycodone compared to the average Florida retailer that Cardinal services. Attachment 2, 4, 16.

77. CVS 219 and 5195, two of Cardinal's top four retail pharmacy customers are located in Sanford, Florida. During 2011, Cardinal Lakeland supplied 6 of the 16 pharmacies with DEA registrations located within the city limits of Sanford, Florida with approximately 3,144,120 dosage units of oxycodone. According to the 2010 U.S. Census Bureau Facts Sheet, Sanford, Florida has a population of 53,570. Based on these numbers, Cardinal Lakeland's distribution of oxycodone could supply every resident of Sanford, Florida with approximately 58.6 dosage units of oxycodone.

78. In 2011, Cardinal collectively distributed 3,144,120 dosage units of oxycodone to six Sanford, Florida pharmacies. Of this volume, Cardinal shipped 3,012,500 dosage units (96%) to the two CVS stores named in the ISO. This volume dwarfs the oxycodone volume purchased by other chain pharmacies in Sanford, such as Walgreens, located in close proximity. *See supra*, ¶ 80; Attachment 17.. An analysis of oxycodone distributions to state populations resulted in the following examples: Michigan averaged 8.26 dosage units per capita; Texas averaged 2.81 dosage units; Louisiana averaged 12.48 dosage units; Illinois averaged 3.69 dosage units, and California averaged 7.98 dosage units. This reflects distributions by all distributors. These states were chosen to give a geographic cross-sample of the United States. Based on this analysis, Cardinal's oxycodone shipments to Sanford would have been sufficient for a population more than 8 times greater than Sanford.

79. In close proximity to CVS 5195, located in Sanford, Florida, which purchased 1.2 million dosage units of oxycodone in 2011, stands a Publix Pharmacy #0641, located at 5240 West State Road 46, Sanford, Florida 32771. The Publix Pharmacy, as

compared to CVS 219, only purchased 25,700 units of oxycodone in 2011. The two pharmacies are located within two (2) miles of one another. Attachment 18.

80. Additionally, in close proximity to CVS 219, located in Sanford, Florida, which purchased 1.8 million dosage units of oxycodone in 2011, stand two pharmacies – Walgreens #6970, located at 3803 S. Orlando Drive, Sanford, Florida, and Wal-Mart Pharmacy #10-0857, located at 3653 Orlando drive, Sanford, Florida. Walgreens #6970 purchased 176,500 dosage units of oxycodone in 2011. Wal-Mart Pharmacy #10-0857 purchased 30,500 dosage units of oxycodone in 2011. Walgreens and Wal-Mart are each located within one (1) mile of CVS 219. Attachment 19.

Inadequate Due Diligence:

81. A comparison of the 2008 ISO/OSC and the 2011 ISO/OSC revealed the same concerns in 2008 and in 2011. Only the specific drugs of abuse had changed. Cardinal completed these high-volume sales without appropriate due diligence to assure that diversion did not occur. The following points outline some of Cardinal's failings:

    a. **Regularly exceeding the distribution thresholds it established for itself.**

        i. Cardinal set monthly thresholds for oxycodone distributions to each of its stores. But from April 2009 to August 2011, Cardinal disregarded the oxycodone thresholds for its top four retailers at least 44 times, sometimes by a few thousand pills and sometimes by tens of thousands. This unexplained disregard for its own thresholds suggests that Cardinal did not take its own policies

seriously.[1] Based on this evidence, DEA was unable to conclude that Cardinal's stated threshold volumes served as a reliable and consistent constraint against diversion.

b. **Failing to follow its own Suspicious Order Monitoring Policies**

i. According to a review of Cardinal's Suspicious Order Monitoring ("SOM") Policies, a site visit is triggered once Cardinal attaches a "red flag" to a particular customer, which is precipitated by the following two events: 1) sales increased by 15% (at least $10,000) and 2) at least 20% or more in dosage units. Once the two events occur, a Cardinal sales person must visit the customer within thirty (30) days to investigate for potential diversion and provide a report to Quality and Regulatory Affairs ("QRA"). Attachment 20.

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[1] Cardinal exceeded its own thresholds ("TH") in the following instances:
Caremed: January 2010 – 37,800 (TH of 26,000); February 2010 – 28,200 (TH of 26,000); March 2010 – 28,000 (TH of 26,000); April 2010 – 34,900 (TH of 32,001); May 2010 – 41,400 (TH 37,000); July 2010 – 67,200 (TH 60,000); September 2010 – 100,200 (TH 75,000); October 2010 – 90,900 (TH 75,000); December 2010 - 134,990 (TH 90,001); January 2011 - 131,920 (TH 90,001); February 2011 – 124,250 (TH 124,000); April 2011 – 149,200 (TH 124,000); May 2011 – 131,720 (TH 124,000).

Gulf Coast: April 2009 – 28,300 (TH 20,000); September 2009 – 18,000 (TH 11,000); November 2009 – 37,700 (TH 33,000); December 2009 – 33,300 (TH 33,000); July 2010 – 115,750 (TH 58,000); August 2010 – 156,100 (TH 95,001); September 2010 – 164,040 (TH 141,000); October 2010 – 144,900 (TH 141,000); March 2011 – 222,800 (TH 207,200); April 2011 – 231,600 (TH 207,200); June 2011 – 279,500 (TH 265,000); August 2011 – 277,380 (TH 265,000).

CVS 219: June 2009 – 118,310 (TH 112,000); August 2009 – 140,500 (TH 112,000); September 2009 – 161,150 (TH 112,000); October 2009 – 135,780 (TH 112,000); December 2009 – 123,000 (TH 118,000); January 2010 – 141,950 (TH 118,000); February 2010 – 142,100 (TH 118,000); March 2010 – 147,600 (TH 140,000); April 2010 – 156,580 (TH 148,000); May 2010 – 172,450 (TH 148,000); June 2010 – 200,000 (TH 148,000); July 2010 – 207,000 (TH 148,000); August 2010 – 242,100 (TH 148,000); September 2010 – 281,600 (TH 235,000).

CVS 5195: June 2010 – 53,300 (TH 27,000); July 2010 – 70,500 (TH 27,000); August 2010 – 108,600 (TH 50,000); September 2010 – 108,800 (TH 105,000); October 2010 – 157,600 (TH 120,000).

ii. Assuming an average cost of $0.75/pill (based on the CVS investigations, CVS told DEA investigators that they sold oxycodone thirty milligram for $1.44/pill), a number of sales would have triggered a "red flag" event under Cardinal's standard operating procedures, thus requiring Cardinal to make an on-site visit within 30 days.[2]

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[2] The following data was taken from Cardinal's ESOM database, provided in response to the AIW, and establishes the following red flag events. The events are based on monthly accruals of controlled substances.

CVS 219:

1. April 2009: CVS purchased 103,390 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
2. June 2009: CVS purchased 126,310 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
3. March 2010: CVS purchased 151,600 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
4. June 2010: CVS purchased 186,000 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
5. August 2010: CVS purchased 242,100 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
6. Cardinal made no site visits to CVS 219 upon these red flag event occurrences.

CVS 5195:

7. June 2010: CVS purchased 43,500 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
8. July 2010: CVS purchased 80,300 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
9. August 2010: CVS purchased 119,400 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
10. October 2010: CVS purchased 157,600 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
11. Cardinal made no site visits to CVS 5195 upon these red flag event occurrences.

Caremed:

c. **No on-site visits for chain retailers**

i. According to DEA review, Cardinal's SOM Policies do not exclude chain retailers from the site-visit requirement. Indeed, the written policies made available to DEA do not indicate any company policy of treating chain retailers differently than independent retailers in terms of the diligence Cardinal's distribution centers are required to conduct.

ii. Cardinal failed to conduct site visits for its retail chain pharmacy customers, thus failing to maintain effective controls to prevent diversion of controlled substances. Cardinal's Suspicious Order Monitoring Policies list "Potential Indicators of Diversion." Many

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12. July 2010: Caremed purchased 67,200 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
13. September 2010: Caremed purchased 100,200 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
14. Cardinal made no site visits to Caremed upon these red flag event occurrences.

Gulf Coast:

15. July 2010: Gulf Coast purchased 115,750 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
16. August 2010: Gulf Coast purchased 156,000 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
17. March 2011: Gulf Coast purchased 222,800 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
18. June 2011: Gulf Coast purchased 279,500 dosage units of oxycodone from Cardinal, which amounted to at least, a 15% increase in sales and at least, a 20% increase in dosage units compared to the previous month.
19. Cardinal made no site visits to Gulf Coast upon these red flag event occurrences.

of these indicators of diversion could only have been ascertained by conducting a site visit.[3]

d. **Low numbers of suspicious orders reported:**

i. Cardinal's electronic suspicious order monitoring system flagged certain orders as suspicious, which required Cardinal to place a "hold" on the order until it decides whether to release the order or to cancel or "cut" the order. From October 1, 2008 through October 26, 2011, Cardinal Lakeland has reported only 41 suspicious orders to DEA. Based on information provided by Cardinal, Cardinal Lakeland suspended sales of controlled substances to 19 DEA registrants from December 1, 2010 through October 26, 2011, at the service of the AIW. Only three of the 41 suspicious orders reported were orders from the 19 customers Cardinal suspended.

ii. Between October 26, 2011 (the day following the execution of the AIWs) and January 31, 2012, Cardinal terminated twenty-eight (28) customers. However, based on DEA's own investigation, during 2010 and 2011, Cardinal continued to sell controlled

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a. Customers of the licensed customer exhibit drug seeking behaviors.
b. Cars full of pharmacy customers.
c. Pharmacy customers who appear to be from outside the reasonable drawing area for the facility.
d. Evidence of illicit drug use around the facility (e.g., used syringes, empty prescription containers).
e. Mailing materials or other evidence of operation of an Internet pharmacy.
f. High ratio of prescriptions for regulated drugs versus other drugs.
g. High ratio of regulated prescription stock to other prescription stock.
h. Primarily cash transactions for regulated drug prescriptions.
i. One employee responsible for the ordering, monitoring, and invoicing of products.
j. High number of customers compared to their peers.
k. For practitioner offices: does the practitioners dispense directly to the public?
l. Lack of auditing processes around purchases.

substances to twelve (12) customers even after Cardinal claimed to have terminated those customers.

iii. Cardinal reported no suspicious orders at either of its CVS facilities or the independent retail pharmacy locations, Caremed and Brooks, except for two suspicious orders made to DEA on December 1, 2011 for CVS 219, well-after the service of the AIW. But DEA records reveal that the stores dispensed prescriptions issued by practitioners that later became the subject of DEA administrative actions, many of which resulted orders suspending the doctors from dispensing controlled substances. Attachment 21.

iv. Following the service of the AIW, from January 1, 2012 through February 3, 2012, the date of service of the ISO, Cardinal reported 173 suspicious orders, none of which concerned its top four retail pharmacy customers.

e. **Mallinckrodt response**

i. After Mallinckrodt's letter, Cardinal contacted CVS's corporate offices and asked that CVS go to three (3) of its pharmacies, including CVS 5195, to ensure that the oxycodone purchases were legitimate. Cardinal had not flagged the high oxycodone sales independently.

DEA Issues Immediate Suspension Order for Cardinal Lakeland

82. Based on the DEA's review of Cardinal's files, DEA's experience and knowledge of Lakeland's distribution practices over time, the 2008 Memorandum of Agreement,

ARCOS data and the information gathered during inspections of Cardinal Lakeland, CVS 219, CVS 5135, Gulf Coast, and Caremed, DEA concluded that "Cardinal failed to conduct meaningful due diligence to ensure that the controlled substances were not diverted into other than legitimate channels, including Cardinal's failure to conduct due diligence of its retail pharmacy chain customers." Attachment 15, at 3. DEA used information about Cardinal Lakeland's failings with regard to its top four retailers to make a broader conclusion about the Lakeland facility's deficiencies as a whole. DEA timed its issuance of the ISO on February 3, 2012, to coordinate with the ISO served on CVS 219 and 5135 the following day, February 4, 2012.

83. Through my training and experience as both a law enforcement officer and as a licensed pharmacist, I believe that the Cardinal Health Lakeland facility's continued DEA registration to handle and distribute any type of controlled substance poses an imminent danger to the public health and safety. I participated in the decision-making process leading up to the issuance of the ISO. The information in all the foregoing paragraphs informed my decision to recommend to the Administrator that an ISO was the appropriate course of action against Cardinal Lakeland.

84. DEA has scheduled an administrative hearing in the Cardinal matter for April 3, 2012. Absent any request for delay by Cardinal and assuming that the Court does not enjoin the ISO, DEA expects to conclude agency proceedings by August.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on: 2/10/12

JOSEPH T. RANNAZZISI

COMPLAINT

EXHIBIT #5

HDMA and NACDS Amicus Brief

Masters Pharmaceuticals v. United States DEA

2016 WL 1321983 (C.A.D.C.) (Appellate Brief)
United States Court of Appeals,
District of Columbia Circuit.

MASTERS PHARMACEUTICALS, INC., Petitioner,

v.

UNITED STATES DRUG ENFORCEMENT ADMINISTRATION, Respondent.

No. 15-1335.
April 4, 2016.

Oral Argument Not Yet Scheduled

Brief for Healthcare Distribution Management Association and National Association of Chain Drug Stores as Amici Curiae in Support of Neither Party

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*II RULE 26.1 DISCLOSURE STATEMENT

Amicus curiae Healthcare Distribution Management Association is a not-for-profit trade association that represents the nation's primary, full-service healthcare distributors. *Amicus curie* National Association of Chain Drug Stores is a nonprofit trade association that represents chain community pharmacy companies, including traditional drug stores, supermarkets, and mass merchants with pharmacies.

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STATUTES, RULES AND REGULATIONS

* Authorities upon which we chiefly rely are marked with asterisks.

*1 INTEREST OF *AMICI CURIAE*

Amicus curiae Healthcare Distribution Management Association (HDMA) is the national, not-for-profit trade association that represents the nation's primary, full-service healthcare distributors.[1] HDMA's members deliver lifesaving products and services, ensuring that 300 million United States consumers have continuous access to prescription drugs and other important products. HDMA's mission is to protect patient safety and access to medicines through the safe and efficient distribution of healthcare products and services. The actual decision to prescribe and dispense these drugs, however, is made by physicians and pharmacists, who use their medical training to assess individual patient needs. Distributors do not see patients, do not have access to individual patient data, and are not trained to make medical decisions about whether a drug should be prescribed or dispensed.

1 As required by Federal Rule of Appellate Procedure 29(c)(5), HDMA and National Association of Chain Drug Stores (NACDS) state that no party's counsel authored this brief in whole or in part, no party or party's counsel contributed money that was intended to fund preparing or submitting the brief, and no person other than HDMA, NACDS, their members, and their counsel contributed money that was intended to fund preparing or submitting this brief. Petitioner Masters Pharmaceuticals, Inc. (Masters) is not an HDMA member and has not otherwise contributed to HDMA for the preparation of this brief or any other purpose. Masters is an associate non-voting member of NACDS, but NACDS does not represent the interests of Masters and Masters has not contributed to the preparation of this brief.

*2 HDMA has 34 distributor members. All of these distributors predominantly buy prescription drugs directly from manufacturers and predominantly distribute them directly to healthcare providers. Nearly all of them (and all that have an interest in this case) are also registered with the Drug Enforcement Administration (DEA) to distribute controlled substances that are contained in prescription drugs. These distributor members have a wide range of business models, including national and regional firms, and publicly traded and family-owned businesses. They include specialty distributors, firms that distribute "biologics" (such as vaccines) or oncology drugs that are often subject to special handling requirements, firms that service only physician offices, and firms that distribute only generic products. While HDMA members have a serious role and responsibilities in drug distribution, distributors do not prescribe or dispense these drugs to patients, and have no direct control over those who do.

Amicus curiae National Association of Chain Drug Stores (NACDS) is a 501(c)(6) nonprofit trade association. NACDS membership consists of chain community pharmacy companies, including traditional drug stores, supermarkets, and

mass merchants with pharmacies - from regional chains with four pharmacies to national companies. NACDS members operate more than 40,000 pharmacies in the United States and employ 179,000 pharmacists. NACDS members fill more than 2.9 billion prescriptions annually and aid patients in taking their medicines *3 correctly and safely, while offering innovative services that improve patient health and healthcare affordability. As dispensers of controlled substances with a corresponding responsibility to guard against abuse and diversion, NACDS members are subject to significant DEA regulation. In connection with their commitment to patient care, NACDS members have zero tolerance for drug abuse and diversion and one hundred percent commitment to legitimate prescription drug access and patient care. The need to balance these two important priorities gives NACDS a significant interest in the important issues raised in this case.

The public health dangers associated with the diversion and abuse of controlled prescription drugs have been well-recognized by Congress, DEA, public health authorities, and others - including HDMA and NACDS and their members. HDMA and NACDS members not only have statutory and regulatory responsibilities to guard against diversion of controlled prescription drugs, but undertake such efforts as responsible members of society. HDMA and NACDS members, however, like all members of the regulated public, also have an interest in receiving notice of their obligations under federal law and, likewise, in the manner in which DEA promulgates, modifies, interprets, and applies its rules. Although HDMA and NACDS take no position on the proper resolution of this case or DEA's findings against Masters Pharmaceuticals, Inc. (Masters), they *4 submit this brief to address the broader concerns of prescription drug wholesale distributors and pharmacies that are raised by the issues presented in this case.

INTRODUCTION AND SUMMARY OF ARGUMENT

Administrative agencies are required to comply with the mandates of the Administrative Procedure Act (APA), 5 U.S.C. § 551 *et seq.* Among other things, that means that an agency is bound by its own regulations. *Environmentel, LLC v. FCC*, 661 F.3d 80, 84-85 (D.C. Cir. 2011). That means that an agency cannot change its position without at least acknowledging and providing a reasoned explanation for the change. *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009). And that means that an agency cannot take a position that conflicts with its existing rules. *Perez v. Mortg. Bankers Ass'n*, 135 S. Ct. 1199, 1209 (2015).

DEA regulations that have been in place for more than 40 years require distributors to *report* suspicious orders of controlled substances to DEA based on information readily available to them (e.g., a pharmacy's placement of unusually frequent or large orders). *See* 21 C.F.R. §§ 1301.71, 1301.74(b). But in certain recent pronouncements, including *Masters Pharmaceuticals, Inc.; Decision and Order*, 80 Fed. Reg. 55,418 (Sept. 15, 2015) (Final Order), DEA has required distributors not only to report suspicious orders, but to *investigate* orders (e.g., by interrogating pharmacies and physicians) and take action to *halt* suspicious orders *5 before they are filled. Those added obligations would significantly expand the "report-only" duty of distributors under the longstanding regulatory scheme and impose impractical obligations on distributors, which occupy a fundamentally different position than the physicians who prescribe the drugs to patients or pharmacists who dispense drugs to fill those prescriptions.

Any attempt to impose such new obligations on distributors would have to be squared with settled administrative law principles. In particular, DEA could not change its position - and impose new obligations on distributors - without first acknowledging the change and providing a reasoned explanation for it. In addition, DEA could not adopt a position that is inconsistent with its own regulations without first engaging in notice and comment and amending its rules. Such notice and comment is not only required to avoid procedural and substantive invalidity, but it would enable DEA to consider the myriad healthcare and patient privacy-related issues raised by such a change in policy, as well as allow DEA to consider alternative, tailored anti-diversion solutions, after hearing from all interested parties, including the members of HDMA and NACDS.

*6 ARGUMENT

I. AN AGENCY'S CHANGE IN POSITION IS INVALID IF THE AGENCY DOES NOT ACKNOWLEDGE THE CHANGE AND PROVIDE A REASONED EXPLANATION FOR IT

1. It is settled that an agency cannot change its position without at least acknowledging and explaining the change. As the Supreme Court has held, an agency must "display awareness that it *is* changing position" and "show that there are good reasons" for the change. *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009); *see also Huerta v. Ducote*, 792 F.3d 144, 153 (D.C. Cir. 2015) ("The Board's position will be deemed 'arbitrary and capricious if it departs from agency precedent without explanation.' " (citation omitted)); *Dillmon v. National Transp. Safety Bd.*, 588 F.3d 1085, 1089-90 (D.C. Cir. 2009) (The APA "requires the agency to acknowledge and provide an adequate explanation for its departure from established precedent."). Agency action that does not do so is "arbitrary and capricious." *Perez*, 135 S. Ct. at 1209.

2. The Controlled Substances Act (CSA), 21 U.S.C. § 801 *et seq.*, allows the Attorney General to register entities to distribute controlled substances if, among other requirements, the distributor maintains "effective controls against diversion of particular controlled substances into other than legitimate medical, scientific, and industrial channels." 21 U.S.C. § 823(b)(1), (e)(1). DEA has promulgated regulations detailing the measures that distributors must take in order *7 to maintain effective controls. Specifically, "[i]n order to determine whether a registrant has provided effective controls against diversion, the Administrator shall use the security requirements set forth in §§ 1301.72-1301.76." 21 C.F.R. § 1301.71(a). Those regulations, in turn, set out explicit requirements for maintaining *physical* security and also, most relevant here, require a registrant to "design and operate a system to disclose to the registrant suspicious orders of controlled substances" and then to report such suspicious orders to DEA. *Id.* § 1301.74(b).

At least until 2006, DEA consistently interpreted Section 1301.71 to require only that distributors *report* suspicious orders. For example, in 1991, DEA issued its Security Outline of the Controlled Substances Act for registrants, "outlin[ing] the steps needed to establish a competent security system which deters diversion and reduces accessibility for potential abusers." *See* Office of Diversion Control, U.S. Department of Justice, *Controlled Substances Security Manual: A Message from the Administrator*, http://www.deadiversion.usdoj.gov/pubs/manuals/ sec/message.htm (last visited Mar. 29, 2016) (*Security Manual*). The *Security Manual* explains in detail the various "steps needed to establish a competent security system which deters diversion," *id.*, but does not include any obligation on the part of distributors to investigate and take action to halt suspicious shipments. Instead, the *Security Manual* states only that a registrant "must design and operate *8 a system to *disclose* suspicious orders of controlled substances" and "must *inform* the appropriate DEA Field Office of suspicious orders immediately upon *discovery*." *Id.*, *Other Security Controls*, http:// www.deadiversion.usdoj.gov/ pubs/manuals/sec/other_sec.htm#sus_orders (emphasis added).

As the Final Order in this case underscores, however, DEA now appears to have changed its position to require that distributors not only *report* suspicious orders, but *investigate* and *halt* suspicious orders. 80 Fed. Reg. at 55,421, 55, 475-77, 55,479. Such a change in agency position must be accompanied by an acknowledgement of the change and a reasoned explanation for it. In other words, an agency must "display awareness that it *is* changing position" and "show that that there are good reasons for the new policy." *Fox Television Stations, Inc.*, 556 U.S. at 515. This is especially important here, because imposing intrusive obligations on distributors threatens to disrupt patient access to needed prescription medications.

3. A senior DEA official has testified in the course of other litigation that DEA made a deliberate decision in 2006-07 "to expand drug wholesalers' obligations" by requiring them - for the first time - to "suspend shipments to a customer if [they] identified an order as suspicious." *United States v. Four Hundred Sixty-Three Thousand Four Hundred Ninety-Seven Dollars & Seventy-Two Cents ($463,497.72)*, 853 F. Supp. 2d 675, 682 (E.D. Mich. 2012) (*United* *9 *States v. $463,497.72*). According to this official, DEA was concerned that this "change in policy" would confuse distributors, "since the prior 'report-only' policy [under 21 C.F.R. §1301.74(b)] had been in place for 35 years." *Id.* [2]

2 Q. And some of those [internal DEA] discussions were about whether or not the industry would be confused by these significant changes, correct?
A. Correct, sir.
Q. And in fact, some of those discussions were about whether your own DEA agents would be confused by these significant changes?
A. Correct, sir. ...
Q. And one of the critical issues of discussion before you did these distributor briefings was, what are we going to tell distributors about this issue of whether to ship or not to ship, correct?
A. Correct.
Q. Because that was a critical issue, correct?
A. Yes, sir.
Q. And you understood at the time that you were making these decisions that it was standard practice in this industry to file suspicious activity reports while continuing to ship products?
A. Yes, sir.
Q. And in the thirty years that this rule had been on the book, the DEA never once said that that was illegal, a violation of DEA rules or regulations or anything, did it?
A. No, sir.
Transcript of Bench Trial at 384:1-8, 386:10-25, *United States v. $463,497.72*, 853 F. Supp. 2d 675, No. 08-11564 (E.D. Mich. Aug. 12, 2011), ECF No. 169 (Testimony of Kyle Wright).

DEA itself maintains that it has not changed its understanding of the regulations notwithstanding the sworn testimony of a DEA official to the contrary.[3] ***10** *See* Final Order, 80 Fed. Reg. at 55,475-76; *see also* DEA Brief 22, *Walgreen Co. v. DEA*, No. 12-1397 (D.C. Cir. Dec. 26, 2012). Yet when establishing criteria for detecting and reporting suspicious orders in 1998, DEA expressly approved a "report only" system. In describing distributors' duties regarding suspicious orders, DEA did not include any responsibility to investigate or halt shipments. According to DEA, the 1998 guidelines were "endorsed by the Attorney General and widely accepted by industry." These guidelines remained in place on DEA's website until as recently as March 28, 2013.

3 Q. You would acknowledge, also, sir, that in 2006 and 2007 there was a significant change in DEA policy, DEA guidance and interpretation on the very issues that are at stake in this litigation, correct?
A. Correct.
Q. That's the suspicious order monitoring process, excessive orders, whether to ship or not, would you agree with me?
A. Yes, sir.
Q. And that was a significant change in your mind?
A. Yes, sir.
Testimony of Kyle Wright at 382:24-383:9.

DEA has pointed to the adjudication in *Southwood Pharmaceuticals, Inc.; Revocation of Registration*, 72 Fed. Reg. 36,487, 36,498-500 (July 3, 2007) (*Southwood*), as evidence that it has previously imposed additional duties. *See* Final Order, 80 Fed. Reg. at 55,476-77 (discussing *Southwood*). In *Southwood*, DEA revoked a distributor's registration based in part on its failure to conduct adequate due diligence on its pharmacy customers. *See* 72 Fed. Reg. at 36,498-500. The decision, however, lacks a clear explanation of a distributor's duties. This is not surprising, given that the decision is the product of an adjudication. As ***11** DEA itself has explained, "the process of adjudication is not well suited" to providing "the regulated community with guidance" as to the scope of a duty. *JM Pharmacy Group, Inc, d/b/a Farmacia Nueva and Best Pharma Corp*, 80 Fed. Reg. 28,667, 28,673 (May 19, 2015). In any event, the salient point is that nowhere does *Southwood* acknowledge any change in interpretation or attempt to explain such change. *See* 72 Fed. Reg. at 36,498, 36,500, 36,502.

DEA stated in a 2006 letter to registrants that the reporting requirement of Section 1301.74(b), "is in addition to, not in lieu of, the general requirement under 21 U.S.C. § 823(e) that a distributor maintain effective controls against diversion."

2006 DEA Letter at 2, *Cardinal Health, Inc. v. Holder*, No. 1:12-cv-00185-RBW (D.D.C. Sept. 27, 2006) (*Cardinal Health*), ECF No. 14-51. The letter also stated that "a distributor has a statutory responsibility to exercise due diligence to avoid filling suspicious orders that might be diverted into other than legitimate medical, scientific, and industrial channels." *Id.* The 2006 letter, however, fails to explain how the statutory command of Section 823(e), a command that the Attorney General consider when adjudicating an application for registration the applicant's "maint[enance] of effective controls against diversion," became a command to registrants to engage in "due diligence" and "avoid filling suspicious orders." *Id.* Moreover, the letter fails to acknowledge that DEA was changing its interpretation or provide any explanation for the change.

***12** In a 2007 letter to registrants sent shortly after *Southwood*, DEA stated that filling suspicious orders without first determining that the orders are not being diverted to illegitimate channels "*may* be failing to maintain effective controls against diversion." 2007 DEA Letter at 2, *Cardinal Health* (Dec. 27, 2007), ECF No. 14-8 (emphasis added). DEA never provided any guidance on when filling a suspicious order would be deemed a failure to maintain effective controls against diversion. Nor did the agency provide any guidance on how a distributor should determine if orders are being diverted to illegitimate channels. And once again, DEA failed to acknowledge, and explain, its change in position.[4]

4 DEA's position continues to evolve. After this Court stayed the Masters Final Order, DEA issued an Order to Show Cause against another distributor, relying on the Masters Final Order to assert that a distributor was obligated to (1) "perform adequate due diligence in investigating its customers and their orders" including obtaining and analyzing a pharmacy's drug utilization report; (2) "obtain the names of any hospices, nursing homes, or physicians for whom [the pharmacy] filled controlled substances"; (3) "investigate the legitimacy of [the pharmacy's] pharmacy practice" to determine whether its customer "is filling legitimate prescriptions"; and (4) consider a geographic area's "prescription drug problem" when filling orders for customers in that area. Order to Show Cause, DEA Docket No. 16-13. This order underscores the importance of the basic administrative law issues presented by this appeal.

An agency's obligation to acknowledge that it is changing position and provide a reasoned explanation for doing so is not a difficult burden to meet. But this requirement nevertheless serves a critical function by ensuring that the agency has actually considered the change, notified the public of the change, and provided ***13** a reasoned explanation for it. In deciding this case, this Court should ensure that DEA has complied with this fundamental requirement.

II. AN AGENCY POSITION IS INVALID IF IT CONFLICTS WITH ITS EXISTING REGULATIONS

1. Even when an agency recognizes and explains a change in position, the new position is still invalid if it conflicts with an existing rule. *See Perez*, 135 S. Ct. at 1207-09; *Am. Mining Cong. v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1109 (D.C. Cir. 1993). In deciding this case, this Court therefore also should consider whether any change in position reflected in the Final Order is inconsistent with existing regulations. In resolving that issue, the key is whether DEA's statement in the Final Order that Masters had a duty not just to *report* suspicious orders but also to *investigate* and *halt* suspicious orders works a substantive change to the preexisting regulations and, thus, is inconsistent with the regulations.[5]

5 A new position, adopted without notice and comment, that conflicts with or is inconsistent with an existing regulation is both *procedurally* and *substantively* invalid. It is procedurally invalid because it amounts to an amendment of a legislative rule without notice and comment. In *Perez*, the Supreme Court held that an agency's change of an *interpretation* (or interpretive rule) does not require notice and comment. 135 S. Ct. at 1206-07. The Court did not disturb, however, the rule that the *amendment* of a regulation requires notice and comment. *See id.* at 1208-09. "[I]f a second rule repudiates or is irreconcilable with a prior legislative rule, the second rule must be an amendment of the first; and, of course, an amendment to a legislative rule must itself be legislative." *Am. Mining Cong.*, 995 F.2d at 1109 (alteration in original) (citation omitted); *see also Ass'n of Flight Attendants-CWA v. Huerta*, 785 F.3d 710, 718 (D.C. Cir. 2015) (reaffirming this rule post-*Perez*). And if the existing regulation is not changed through notice and comment, the new, inconsistent, position is substantively invalid because an

agency "must comply with its own regulations." *Environmentel, LLC v. FCC*, 661 F.3d 80, 84-85 (D.C. Cir. 2011); *see also Associated Builders & Contractors, Inc. v. Herman*, 166 F.3d 1248, 1255-56 (D.C. Cir. 1999) (setting aside agency action for failure to adhere to regulations).

***14** 2. a. Section 1301.71 by its terms restricts DEA's authority to delineate the requirements for "effective controls" - stating that, in evaluating a control system, the Administrator "*shall use* the security requirements set forth in §§ 1301. 72-1301.76." 21 C.F.R. § 1301.71(a) (emphasis added). Nothing in Sections 1301.72-1301.76 requires distributors to investigate the legitimacy of orders, or to halt shipment of any orders deemed to be suspicious.

Instead, Sections 1301.72-1301.76 make clear that a distributor's due diligence obligations are limited to (1) conducting a "good faith inquiry" to verify that the customer has a valid DEA registration, *see* 21 C.F.R. § 1301.74(a); and (2) operating a system to identify suspicious orders and inform DEA of such orders, *see Id.* § 1301.74(b). And while some regulations explicitly ban distributors from actually transferring controlled substances in certain circumstances - *see id.* § 1301.74(a), (d), (g) - there is no prohibition on shipment of suspicious orders. The fact that Section 1301.71(a) specifically and explicitly requires the Administrator to use only certain provisions to judge compliance indicates that it prohibits DEA from utilizing *other* criteria not listed in the regulation.

***15** This follows from a straightforward application of the *expressio unius est exclusio alterius* principle (expression of one thing is the exclusion of the other). *See, e.g., U.S. Term Limits, Inc. v. Thornton*, 514 U.S. 779, 782, 793 n.9 (1995) (requirement that Members of House of Representatives "shall" meet specific eligibility requirements bars Congress from adopting additional requirements beyond those specifically mentioned in the text); *Lewis v. Alexander*, 685 F.3d 325, 347 (3d Cir. 2012) (rejecting effort to impose new criteria for certain trusts beyond those explicitly set forth in statute because "where a specific list is set forth, it is presumed that items not on the list have been excluded"), *cert. denied*, 133 S. Ct. 933 (2013); *see also TRW Inc. v. Andrews*, 534 U.S. 19, 28-29 (2001).

This Court has applied the *expressio unius* principle to limit agency discretion in analogous circumstances. In *Ethyl Corp. v. EPA*, the Court considered the meaning of 42 U.S.C. § 7545(f)(4), a provision that empowered the EPA Administrator to waive a statutory ban on certain new fuel additives. 51 F.3d 1053 (D.C. Cir. 1995). The only criterion that the statute explicitly required the Administrator to consider in assessing a waiver request was whether the fuel additive would affect compliance with emission standards. 42 U.S.C. § 7545(f)(4). Because the statute did not *explicitly* bar the Administrator from considering other criteria not mentioned in § 7545(f)(4), the Court examined whether the ***16** enumeration of only one specific criterion *implicitly* barred the Administrator from denying a waiver based on other factors - and concluded it did.

The Court explained that "[t]he plain language of the provision makes clear that waiver decisions are to be based on one criterion." *Ethyl Corp.*, 51 F.3d at 1058. By basing her waiver decision on public health implications, even though "[n]owhere in th[e] waiver provision is there any mention of applicants establishing or the Administrator determining a fuel additive's effect on public health," the Administrator had acted contrary to the language of the statute. *Id.* In short, EPA could not properly "apply criteria beyond those prescribed in the statute in enforcing the waiver provision," despite the lack of any explicit statutory bar on doing so. *Id.* at 1059. In fact, the Court thought that the statute so "unambiguously" prohibited consideration of "additional criteria" that it refused to grant EPA *Chevron* deference. *Id.* at 1058-60.

This case is different in one important respect. The statute in *Ethyl Corp authorized* the EPA Administrator to waive certain prohibitions if the fuel additive would not affect compliance with emission standards - providing that the Administrator "*may* waive" if that condition were met. 42 U.S.C. § 7545(f)(4) (emphasis added). By contrast, the regulation here states that the administrator "*shall* use" particular requirements (i.e., those listed in Sections 1301.72-1301.76). ***17** If anything, that distinction should strengthen the force of the *expressio unius* principle here.[6]

6 Although *Ethyl Corp.* involved the interpretation of a statute, the *expressio unius* principle applies in interpreting regulations as well. *See, e.g., United Dominion Indus., Inc. v. United States*, 532 U.S. 822, 836 (2001); *Fulani v. Fed. Election Comm'n*, 147 F.3d 924, 928 (D.C. Cir. 1998).

b. Other regulations reinforce this interpretation. When the agency promulgated Section 1301.71, DEA simultaneously enacted other provisions that explicitly gave the Administrator broad authority to consider more than the enumerated criteria. For example, 21 C.F.R. § 1301.34(c) instructs DEA on how to determine whether importers of controlled substances are satisfying their antidiversion obligations. In stark contrast to Section 1301.71(a), Section 1301.34(c) explicitly allows the Administrator to consider additional criteria beyond those specifically listed in the regulations. 21 C.F.R. § 1301.34(c). ("In determining whether [an importer] can and will maintain effective controls against diversion ..., the Administrator shall consider *among other factors*: (1) Compliance with the security requirements set forth in §§ 1301.71-1301.76 ...." (emphasis added)).

Similar catch-all formulations appear throughout the DEA regulations. At least nine other provisions require the Administrator to consider certain specifically-enumerated criteria when making a particular decision or determination, yet also include a catch-all provision expressly authorizing her to ***18** consider other, non-enumerated, criteria.[7] These provisions suggest that when the DEA regulations intend to grant the Administrator leeway to consider additional, unspecified criteria, they do so explicitly. *See Ethyl Corp.*, 51 F.3d at 1061 (concluding that agency had wrongly considered public health, which the statute did not list as a criterion, in making a waiver determination, when another nearby provision explicitly instructed the agency to consider public health); *see also Bates v. United States*, 522 U.S. 23, 29-30 (1997) ("Where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion." (citation omitted)).

7 *See, e.g.*, 21 C.F.R. §§ 1301.34(b), 1301.74(c), 1301.76(b), 1303.11(b), 1303.13(b), 1310.10(d), 1310.21(c), 1315.11(b), 1315.13(b).

Similarly, the presence of express bans on transferring controlled substances in certain circumstances in other provisions strongly indicates that no such ban applies to shipping suspicious orders. The DEA regulations clearly and explicitly specify the precise circumstances in which a distributor is prohibited from transferring controlled substances. *See, e.g.*, 21 C.F.R. § 1301.74(a) (barring transfers "to any person who the registrant does not know to be registered to possess" the substance unless the distributor first has made "a good faith inquiry" as to whether the recipient possesses such registration); *Id.* § 1301.74(d) (barring ***19** certain transfers of free samples of drugs); *Id.* § 1301.74(g) (barring certain transfers of specific chemicals). There is no such requirement in Section 1301.71.

c. The regulatory history also indicates that Section 1301.71(a)'s second sentence was intended to clarify that a distributor's compliance with Sections 1301.72-1301.76 satisfies its anti-diversion obligations.

The Justice Department originally proposed draft regulations to implement the CSA in 1971. *See Regulations Implementing the Comprehensive Drug Abuse Prevention and Control Act of 1970*, 36 Fed. Reg. 4928 (Mar. 13, 1971). The draft of Section 301.91 (the predecessor to Section 1301.71) included the statutory requirement that registrants maintain effective controls against diversion, but it did *not* explicitly limit the Administrator to any particular criteria when assessing compliance. *Id.* at 4935. Instead, it noted that the security regulations (which would eventually become Sections 1301.72-1301.76) were "intended as standards for the construction and maintenance of security facilities ... [and] [s]ubstantial compliance with these standards may be deemed sufficient by the Bureau after evaluation of the overall security controls." *Id.* at 4935.

In the final rule, however, the Justice Department eliminated this grant of discretion and instead mandated that the Administrator "*shall* use the security requirement set forth" as standards. *See* ***20** *Regulations Implementing the*

Comprehensive Drug Abuse Prevention and Control Act of 1970, 36 Fed. Reg. 7776, 7784 (Apr. 24, 1971) (emphasis added). The next sentence of the final rule is roughly the same as it was in the proposed rule, explaining that "[s]ubstantial compliance with these standards may be deemed sufficient by the Director after evaluation of the overall security system and needs of the applicant or registrant." *Id.* Thus, the Department replaced a sentence that gave the Administrator discretion by noting that the regulations were only "intended as standards" with a sentence that mandated that the Administrator "shall use" the enumerated regulations to determine compliance. *See United States v. Monzel*, 641 F.3d 528, 531 (D.C. Cir. 2011) (noting that word "shall" imposes a requirement that is "mandatory," "imperative," and "not merely precatory" (citation omitted)).

3. In addition to introducing a duty to *investigate* and *halt* suspicious orders, the Masters Final Order also expands the definition of "suspicious order" to include "the pharmacy's business model, dispensing patterns, or other characteristics that might make an order suspicious, *despite the particular order not being of unusual size, pattern or frequency*." *See* Final Order, 80 Fed. Reg. at 55,473-74 (emphasis added) (citation omitted). This transforms the duty set forth in the regulations to report suspicious *orders* into a duty to investigate suspicious *customers*. A requirement to report orders placed by customers with suspicious "business models" or another undefined customer-specific suspicious "characteristic," when the underlying order itself is "not ... unusual" conflicts with ***21** the regulation's focus on "suspicious *orders*" and the regulation's clarifying language that, in determining whether an order is suspicious, registrants should look for "orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency," *i.e.*, order-specific information. 21 C.F.R. § 1301.74(b) (emphasis added). Additionally, the catch-all, "other characteristics" category included in the new definition of "suspicious order" is vague and open-ended, and would allow DEA to retroactively point to any orders that it has determined to be suspicious after the fact and penalize registrants for failing to report them *ex ante*.

If the Court concludes that the Masters Final Order works a substantive change to DEA's regulations in these important respects, then the agency's imposition of these new duties and criteria would require notice and comment. [8]

8 To the extent that Masters agreed in its Memorandum of Agreement (MOA) with DEA to undertake obligations that are not imposed by the CSA and DEA's regulations, those obligations are not binding on distributors. If this Court determines that Masters failed to abide by its MOA, the Court should make clear that Masters' obligations under its MOA do not apply to other distributors. Nor are they appropriate factors for DEA to consider when determining whether other distributors maintain effective controls against diversion.

***22 III. APPLYING THESE SETTLED ADMINISTRATIVE LAW PRINCIPLES IS ESPECIALLY IMPORTANT HERE**

The practical infeasibility of requiring distributors to investigate and halt suspicious orders (as well as report them) underscores the importance of ensuring that DEA has complied with the APA before attempting to impose such duties.

Different entities supervise the discrete links in the chain that separates a consumer from a controlled substance. Statutes and regulations carefully define each participant's role and responsibilities. First, a patient explains his symptoms to a doctor. Second, the doctor applies her medical training and expertise to decide which medication, and in what amount, would best address that patient's healthcare needs and issues an appropriate prescription. Third, a pharmacy receives the prescription and, after a pharmacist applies her training, may dispense the medication to the patient. Fourth, in order to stock its inventory, a pharmacy purchases controlled substances from a wholesale distributor.

The orders that a pharmacy places with a distributor are based on many factors including patient needs, the pharmacy's existing inventory, potential drug shortages, pricing, cash flow, and anticipated need during weekends and holidays. A Schedule II order form (DEA Form 222) includes only the pharmacy's name, address, DEA registration number, and the

amount of the substance the pharmacy *23 wishes to buy.[9] *See* Sample DEA Form 222, Addendum. Order forms do not contain any patient information and distributors do not and cannot know the identity of patients who received or will receive the medications dispensed by a pharmacy. Pharmacies may purchase different drugs from different distributors, or even the same drug from multiple distributors. The volume of controlled substances ordered by a pharmacy is affected by numerous factors including its proximity to or affiliation with medical facilities, the availability of other pharmacies in the area, participation in a pharmacy benefit management plan, and the hours of operation.

9 DEA 222 Order forms are used solely for Schedule II controlled substances. Other controlled substances (Schedules III-V) can be ordered without this form. The information provided in ordering those products by a pharmacy from a wholesaler remains the same (*i.e.*, pharmacy's name, address, DEA registration number, and the amount of the substance the pharmacy wishes to buy).

Distributors are legally prevented from sharing how much of a given drug or product each is selling to a given pharmacy without potentially violating antitrust laws. Without such information, an individual wholesale distributor cannot know what other entities its pharmacy customer may be purchasing from, and how much total product the customer is purchasing. Similarly, for competitive and antitrust reasons, pharmacies have been reluctant to disclose purchases made from different wholesalers. Thus, a single distributor has no reliable way of determining with *24 certainty if it is a pharmacy's sole supplier of controlled prescription drugs or if that pharmacy is purchasing controlled prescription drugs from any number of other distributors. And HDMA members cannot, without risk of violating the antitrust laws, pool their sales data to determine the totality of a pharmacy's orders and assess whether the total orders are indicative of diversion occurring as a result of the conduct of prescribers, their patients, or pharmacies.

At the same time, distributors lack access to data governing individual patients, and individual doctor-patient and pharmacist-patient decisions - information that, understandably, is carefully guarded by privacy laws. Likewise, distributors lack the means to compel information from prescribers and dispensers regarding the ultimate consumer. Wholesale drug distributors, who are not licensed healthcare professionals, may not lawfully gain access to a patient's medical information, including his or her pharmacy records of controlled substance prescriptions. Physicians and pharmacists are precluded from using or disclosing a patient's personal medical information absent the patient's specific written "authorization," or in certain limited circumstances not relevant here. 45 C.F.R. §§ 164.502(a), 164.506(a), (c). It is not feasible for distributors to reliably detect diversion without this information, but they lack access to the information. DEA, however, does have access to this information - or at least the legal authority to obtain it. Accordingly, DEA's regulations had sensibly imposed a duty on *25 distributors simply to *report* suspicious orders, but left it to DEA and its agents to investigate and halt suspicious orders.

Distributors take seriously their duty to report suspicious orders, utilizing both computer algorithms and human review to detect suspicious orders based on the generalized information that *is* available to them in the ordering process. A particular order or series of orders can raise red flags because of its unusual size, frequency, or departure from typical patterns with a given pharmacy. Distributors also monitor for and report abnormal behavior by pharmacies placing orders, such as refusing to provide business contact information or insisting on paying in cash.

As the existing regulations recognize, other entities and individuals in the healthcare system are better positioned to investigate and assess the legitimacy of prescriptions and take steps to halt diversion. For example, the regulations require physicians and pharmacists - but not distributors - to assume "responsibility" for "proper prescribing and dispensing" of prescription drugs. 21 C.F.R. § 1306.04(a). That regulation accords with the fact that physicians and pharmacists are providing direct patient care, including prescribing and dispensing particular medications related to their respective roles with the patient, and have access to the individual patient information necessary to provide that care. Distributors, by contrast, are not professionally trained as physicians or pharmacists and have no relationship or contact with individual patients. There is simply no practical way for distributors *26 to look over the shoulder of pharmacists and double-check the validity of each prescription in light of an individual patient's circumstances.

At the same time, while all agree that abusive practices should be stopped, there is also a countervailing concern: ensuring that patients who legitimately need medication have ready access to it, after it is prescribed. Imposing a duty on distributors - which lack the patient information and the necessary medical expertise - to investigate and halt orders may force distributors to take a shot-in-the-dark approach to complying with DEA's demands. That approach, in turn, could restrict patients' access to drugs for legitimate medical needs. *See, e.g.*, Pat Anson, *Fear of DEA Causing Drug Shortages*, Pain News Network (June 30, 2015), http://www.painnewsnetwork.org/stories/2015/7/30/fear-of-dea-causing-drug-shortages.

Given the unique role that distributors occupy in the healthcare system, any attempt to impose additional obligations on them to investigate and halt suspicious orders would raise serious policy and practical issues, such as the disruption of patient access to prescribed medications. Those issues at a minimum warrant *27 careful and public deliberation, which is exactly what administrative law principles call for when agencies seek to change the existing rules. [10]

10 At a minimum, given the far-reaching issues raised by the imposition of such obligations on distributors generally, if this Court does conclude that the Final Order in this case may be upheld even as to any new duties that it imposes, HDMA and NACDS urge this Court to make clear that its decision (like the Final Order) is based on the particular circumstances presented by Masters' conduct, including its alleged failure to follow its own procedures.

*28 CONCLUSION

In deciding this case, the Court should ensure that DEA has complied with the administrative law principles discussed herein.

Appendix not available.

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COMPLAINT

EXHIBIT #6

HDMA Amicus Brief

Cardinal Health, Inc. v. United States DOJ

2012 WL 1637016 (C.A.D.C.) (Appellate Brief)
United States Court of Appeals,
District of Columbia Circuit.

CARDINAL HEALTH, INC., Plaintiff-Appellant,

v.

UNITED STATES DEPARTMENT OF JUSTICE, et al., Defendants-Appellees.

No. 12-5061.
May 9, 2012.

On Appeal from the United States District Court for the District of Columbia
Oral Argument Not Yet Scheduled

Amicus Curiae Brief of Healthcare Distribution Management Association in Support of Appellant Cardinal Health, Inc.

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*V CORPORATE DISCLOSURE STATEMENT

Pursuant to Rule 26.1, Federal Rules of Appellate Procedure, Movant/Proposed *Amicus Curiae* Healthcare Distribution Management Association does not have a parent corporation, and does not have any corporate stock.

*vii TABLE OF CONTENTS

*viii TABLE OF AUTHORITIES

Except for 42 U.S.C. § 1395x, 45 C.F.R. §§ 160.103,164.502, and 164.506, all applicable statues and regulations are contained in the Brief for Appellant.

Statutes and Regulations

Rules

*1 Pursuant to the concurrently filed Motion for Leave To File *Amicus Curiae* Brief, Healthcare Distribution Management Association ("HDMA") respectfully submits this brief in support of Appellant Cardinal Health, Inc. ("Cardinal Health").

I. STATEMENT OF INTEREST

Amicus curiae HDMA is the national, not-for-profit trade association that represents the nation's primary, full-service healthcare distributors. [1] These healthcare distributors deliver lifesaving products and services, ensuring that 300 million U.S. consumers have continuous access to prescription drugs and other important products. Prescription drugs are rarely shipped from the manufacturer straight to the pharmacy or other healthcare provider. Rather, most prescription drugs are sold by manufacturers to distributors that ensure that nine million products are safely and efficiently delivered to 200,000 pharmacies, hospitals, clinics, physician offices, nursing homes, government providers, and others each and every day.

1 As required by Fed. R. App. P. 29(c)(5), HDMA states that no party's counsel authored this brief in whole or in part, no party or party's counsel contributed money that was intended to fund preparing or submitting the brief, and no person other than HDMA, its members, and its counsel contributed money that was intended to fund preparing or submitting this brief. HDMA member Cardinal Health does pay organizational dues to HDMA set by formula, but funding for this brief was provided out of general operating revenues and not by any special assessment on the membership.

*2 HDMA has 34 distributor members. All of these distributors predominantly buy prescription drugs directly from manufacturers and predominantly distribute them directly to healthcare providers. Nearly all of them (and all that have an interest in this case) are also registered with the U.S. Drug Enforcement Administration (DEA) to distribute prescription drugs containing controlled substances (hereinafter "controlled prescription drugs"). These distributor members have a wide range of business models, including national and regional firms, and publicly traded and family-owned businesses. They include specialty distributors, firms that distribute only "biologies" (such as vaccines) or oncology drugs, firms that service only physician offices, and firms that distribute only generic products.

HDMA's members have not only statutory and regulatory responsibilities to detect and prevent diversion of controlled prescription drugs, but undertake such efforts as responsible members of society. The public health dangers associated

with the diversion and abuse of controlled prescription drugs have been well-recognized over the years by Congress, DEA, HDMA and its members, and public health authorities.

HDMA's members are one of the principal groups of businesses affected by Congressional and DEA efforts to regulate the distribution of controlled prescription drugs. To assist the Court in reviewing the parties' respective actions *3 in this matter, HDMA respectfully provides the context in which DEA has taken enforcement actions against distributors while, at the same time, the agency has failed to provide meaningful guidance to assist the regulated industry in complying with DEA's interpretation of its implementing regulations. HDMA respectfully submits that, despite the agency's oft-recited refrain that the regulations are "clear," the regulated industry does not know the rules of the road because DEA has not adequately explained them.

DEA issued an Immediate Suspension Order ("ISO") against Cardinal Health based, in pertinent part, upon an alleged failure to maintain an effective program designed to detect and prevent diversion of controlled prescription drugs and an alleged failure to design and operate a system to detect and report suspicious orders as required by 21 C.F.R. §§ 1301.71 and 1301.74(b). HDMA's interest in this matter on behalf of its wholesale drug distributor members is this: a regime under which *any* wholesaler can summarily lose its DEA registration by an ISO *at any time* regardless of its programs to detect and prevent diversion of controlled prescription drugs and its systems to detect and report suspicious orders would constitute arbitrary and capricious decision making by the agency and lack due process.

*4 This case examines only the judgment of the court below in failing to preserve the status quo until the merits of DEA's administrative action against that registration can be decided in the Order To Show Cause proceeding. HDMA, however, wishes to express through this *amicus curiae* brief the grave concerns of the regulated industry that the process used by DEA in this matter, an ISO that deprives a wholesale distributor of the ability to distribute controlled prescription drugs prior to a hearing, is wholly inappropriate given the bare allegations of the ISO. DEA places a burden - discerning when diversion may occur beyond the DEA-registered and state-licensed prescribing practitioner and DEA-registered and state-licensed dispensing pharmacist - on wholesale distributors of controlled prescription drugs without providing meaningful guidance or tools that would enable the regulated industry to maintain compliance. Moreover, this regulatory liability shift is contrary to DEA's own regulations and policy regarding the responsibilities of practitioners and pharmacists to ensure that controlled prescription drugs are prescribed and dispensed only for legitimate medical purposes in the ordinary course of professional practice.

II. HDMA HAS UNDERTAKEN SIGNIFICANT EFFORTS TO OBTAIN GUIDANCE ON DIVERSION PREVENTION FROM DEA AND TO PROVIDE GUIDANCE TO ITS MEMBERS

HDMA has engaged in extensive efforts to obtain guidance from DEA and developed guidance for HDMA members on diversion prevention. In 2007, as *5 DEA was issuing a series of letters to all distributor registrants, HDMA began a series of meeting requests to DEA's Office of Diversion Control to discuss what concrete steps HDMA members could take to maintain compliance with their statutory and regulatory obligations as registrants. DEA met with HDMA on numerous occasions regarding diversion prevention. *See* Declaration of Joseph Rannazzisi, Joint Appendix (JA) 72 (hereinafter "Rannazzisi Dec.")) at ¶ 37.

A. PUBLICATION OF HDMA'S INDUSTRY COMPLIANCE GUIDELINES

In late 2007, HDMA began development of its publication "Industry Compliance Guidelines: Reporting Suspicious Orders and Preventing Diversion of Controlled Substances." Appendix A.[2] A committee of HDMA members contributed to the development of this publication. The Industry Compliance Guidelines ("ICG") contained the following elements:

2 The Industry Compliance Guidelines have been available on HDMA's website since publication. *http://hdmanet.org/gov_affairs/pdf_controlled/20081113_icg.pdf*.

I. Know Your Customer Due Diligence
II. Monitoring for Suspicious Orders

III. Suspend/Stop an Order of Interest Shipment

IV. Investigation of Orders of Interest

V. File Suspicious Order Reports With DEA

VI. Employees, Training and Standard Operating Procedures (SOPs)

VII. Additional Recommendations

The ICG was not crafted to be overly prescriptive; rather, it was designed to ensure that proper consideration was paid to the host of factors a wholesale drug *6 distributor must face in evaluating orders for controlled prescription drugs. Under the ICG, when information indicates that further investigation is warranted, the first obligation is to look into the potential concern, not to drown DEA in a flood of suspicious order reports that may be otherwise explainable. The ICG also calls for documentation of procedures and their implementation and urges HDMA members to maintain robust compliance systems. Noteworthy elements include:
• Periodic internal audits of suspicious orders, compliance procedures and results;

• Periodic reviews and revisions of internal standard operating procedures for compliance with 21 C.F.R. §§ 1301.71(a) and 1301.74(b) and any new DEA guidance, as well as employee training requirements/procedures; and

• Periodic review of the distributor's system for monitoring for suspicious orders, including the system design and the thresholds, to determine whether revisions should be developed.

A draft of the voluntary guidance was presented to the DEA Office of Diversion Control and the DEA Office of the Chief Counsel in the spring of 2008 for their review and comment. The voluntary guidance was revised in light of DEA's comments and the current edition was published in the fall of 2008. On *7 October 17, 2008, the DEA Chief Counsel wrote to HDMA, stating in pertinent part:
The Drug Enforcement Administration (DEA) commends the efforts of the Healthcare Distribution Management Association (HDMA) to assist its membership to fulfill their obligations under the Controlled Substances Act and implementing regulations. The elements set forth in the "Industry Compliance Guidelines: Reporting Suspicious Orders and Preventing Diversion of Controlled Substances" are important to sustaining effective controls to guard against diversion of controlled substances....

Although diversion control is not a "one size fits all" effort, companies that implement processes and procedures that effectively accomplish these objectives will do much to ensure that vital controlled substances are not diverted to illegitimate uses.

Appendix B.[3] HDMA has also held education sessions and numerous discussions on the Industry Compliance Guidelines.

3 Appendix B has been posted on the HDMA website since publication of the ICG. *http //hdmanet.org/gov_affairs/pdf_controlled/20081113_dealetteronicg.pdf*

B. HDMA REQUESTS TO DEA FOR ARCOS DATA AND OTHER INFORMATION

In the district court below, and in support of the Opposition to Plaintiffs Motion for Preliminary Injunction, defendants submitted the affidavit of the DEA ***8** Deputy Assistant Administrator for the Office of Diversion Control.[4] That affidavit reads, in pertinent part:

4 As discussed *infra* at note 5 and accompanying text, HDMA fully supports Appellant's argument that the DEA submissions before the district court are *post hoc* rationalizations and the district court erred in relying on those submissions.

> Customers ordering the same controlled substances from multiple distributors may be indicative of diversion due to the customer ultimately acquiring large amounts of controlled substances through multiple sources. Distributors are unable to access other distributor's [sic] information regarding distributions due to the proprietary nature of the information. The customer having multiple sources of distribution may avoid scrutiny by maintaining several sources to obtain controlled substances.

Rannazzisi Dec, JA 70 at ¶ 32. DEA, on the other hand, has access to this information because all distributors are required to report, relevant to this instant matter, distribution of Schedule II controlled substances and Schedule III narcotics directly to DEA under the Automated Reports and Consolidated Orders System (ARCOS). 21 C.F.R. § 1304.33.

HDMA respectfully submits that this information would be extremely important to distributors who are attempting to discern the *bona fides* of their customers. A customer receiving controlled substances from multiple sources would certainly be an appropriate subject of at least additional scrutiny. In February 2009 in a meeting with DEA's Office of Diversion Control, HDMA requested that distributors be permitted access to aggregated ARCOS data so as to ***9** disclose whether any customers were receiving ARCOS-reportable controlled substances from multiple sources. When DEA asserted that such data contained proprietary information, HDMA indicated at that time that the requested data could be aggregated or otherwise masked to address concerns regarding proprietary information. Although DEA responded that the agency was looking into the matter, it has not provided any such aggregated data.

Another meeting between HDMA and the Office of Diversion Control was held on December 7, 2010. HDMA reiterated its request for aggregated ARCOS data and sought to have DEA clarify its position on the agency's authority and willingness to respond to inquiries by registrants about customer ordering patterns based on information available to DEA. DEA indicated its concern that, even when aggregated, individual distributors' data might be identifiable and has not provided the requested data. *See* Summary of DEA-HDMA Meeting Held on December 7, 2010, JA 299.

After the December 2010 meeting, HDMA undertook a comprehensive assessment of member companies' questions and concerns with the current suspicious order monitoring requirements. On June 1, 2011, HDMA provided DEA with a series of questions seeking further guidance regarding concrete suggestions for improving diversion prevention and HDMA's summary of the December 2010 meeting with DEA. HDMA letter to DEA, (June 1, 2011), JA ***10** 285. Although there has been informal communication between HDMA and DEA regarding this course of correspondence, the agency has yet to answer HDMA's June 1, 2011, requests and questions.

III. IN THE ABSENCE OF APPROPRIATE GUIDANCE FROM DEA, REGISTRANTS FACE A COMPLIANCE BURDEN THAT IS IMPOSSIBLE TO MEET

HDMA wishes to underscore, in the strongest possible terms, its support for DEA's mission to prevent diversion of prescription controlled drugs. The societal costs of prescription drug abuse are huge, and the development and implementation of practices and procedures to detect and prevent diversion are burdens that HDMA members willingly bear. HDMA respectfully submits that the instant matter provides an object lesson that regardless of what diversion control programs a registered wholesale distributor may institute, DEA can summarily suspend the registration without adequate process.

In DEA's view, which was reiterated at the February 29, 2012, hearing below, the sheer volume of product reported to DEA under ARCOS should be indicative of diversion. This view does echo agency guidance from December 2007: "The size of an order alone, whether or not it deviates from a normal pattern is enough to trigger the registrant's responsibility to report the order as suspicious." *See* Rannazzisi Dec, JA 70 at ¶ 33 (quoting December 27, 2007 *11 letter to registrants). While consistent, it is unhelpful. An order in a "normal pattern" is the antithesis of a "suspicious order." [5]

5 HDMA fully supports Appellant's argument that the DEA submissions before the district court are *post hoc* rationalizations and the district court erred in relying on those submissions. Citation to the Rannazzisi Declaration underscores the dilemma faced by wholesale distributors. Whereas some agency pronouncements have emphasized a host of factors that DEA believes should be considered, when it comes to issuance of an ISO, DEA now asserts that size alone can be determinative of a "suspicious" order.

DEA is requiring wholesale distributors to assume responsibilities while denying them the opportunity to make meaningful choices in fulfilling those responsibilities. Wholesale distributors cannot know, based upon any one factor, whether product that leaves their control is to be prescribed by DEA-registered and state-licensed practitioners and dispensed by DEA-registered and state-licensed pharmacists only for legitimate medical purposes.

DEA's reliance on volume as the touchstone for wholesale distributors is without merit. In DEA's own Policy Statement on Dispensing Controlled Substances for the Treatment of Pain, the agency abjures reliance on any single factor, including quantities of controlled substances prescribed, in determining whether prescriptions for controlled substances are "only for legitimate medical purposes in the usual course of professional practice." 71 Fed. Reg. 52,715, 52,720 cols. 2-3 (Sept. 6, 2006). Moreover, DEA's own regulations place the responsibility for lawful prescribing and dispensing of controlled substances on the *12 two learned intermediaries who come after wholesale distributors in the supply chain. "The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription." 21 C.F.R. § 1306.04(a).

In a recent final order revoking a practitioner's registration, the DEA Administrator adopted the Chief Administrative Law Judge's finding that absolute and comparative statistical information regarding purchasing trends of Schedule II and Schedule III narcotics associated with the practitioner's practice, without context, was not probative of whether revocation was in order. *Carlos Gonzalez, M.D., Decision and Order,* 76 Fed. Reg. 63,118, 63,138, cols. 2-3 (Oct. 11, 2011) (final order revoking registration despite rejection of evidence as to volume).

Even if wholesale drug distributors wanted to review and assess a patient's medical information, including his or her pharmacy records of controlled substance prescriptions, it is not legally permissible for them to do so. In late 2000, the U.S. Department of Health and Human Services ("HHS"), pursuant to the authority granted by the Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), issued final regulations regarding " *13 Standards For Privacy Of Individually Identifiable Health Information." 65 Fed. Reg. 82,462 (Dec. 28, 2000) (the "Privacy Rule"). [6] The Privacy Rule applies to so-called "covered entities," defined as: a health plan, a health care clearinghouse, or a health care provider that "transmits any health information in electronic form in connection with" a HIPAA-covered transaction. 45

C.F.R. § 160.103. Like physicians, pharmacists are deemed to be health care providers under HIPAA and are, therefore, covered entities. 42 U.S.C. §§ 1395x(s), (u). [7]

6 Those regulations were substantially revised nearly two years later. 67 Fed. Reg. 53,182 (Aug. 14, 2002).

7 *See also* U.S. Dept. of Health & Human Services, *Health Information Privacy*, available at: *http:// www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/index.html* (accessed Feb. 21, 2012).

Covered entities are precluded from using or disclosing a patient's "protected health information" ("PHI") (*i.e.*, "individually identifiable health information") absent a patient's specific written "authorization," or in certain limited circumstances not relevant here. 45 C.F.R. § 164.502(a)(1); *see also* 45 C.F.R. § 164.506(a) and (c); 45 C.F.R § 164.502(a)(1)(H) ("[a] covered entity may not use or disclose protected health information, except ... to carry out treatment, payment, or health care operations ...."). None of the relevant exceptions apply to a wholesale drug distributor fulfilling orders received from a retail pharmacy. There is, therefore, no basis upon which a wholesale distributor ***14** could obtain access to patient PHI through the pharmacy - its covered entity business partner.

However serious a problem that prescription drug abuse is, the control of it cannot rest alone on the wholesale distributor that has neither the ability nor opportunity to review the individual patient or the practitioner's and pharmacist's interaction with that patient. Moreover, according to the Substance Abuse and Mental Health Services Administration (SAMHSA), among persons aged 12 or older in 2009-2010 who used pain relievers nonmedically in the past 12 months, 55.0 percent got the drug they most recently used from a friend or relative for free. [8] Such diversion is beyond the power of a wholesale distributor to detect or prevent. Suspension or revocation of a wholesale distributor's DEA registration cannot address this serious problem.

8 Substance Abuse and Mental Health Services Administration, "Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings," *available at http:// www.oas.samhsa.gov/NSDUH/2k10NSDUH/2k10Results.pdf*, at 2.

DEA's goal, the prevention of diversion of controlled prescription drugs, is, of course, a public good. HDMA and the regulated industry have been seeking, and will continue to seek, ways to work toward this goal. The regulator, however, should not be permitted to sanction the regulated without a hearing based upon factors that the agency itself has previously found to be not determinative. HDMA readily acknowledges that legal investigation and law enforcement must be carried ***15** out in a manner that protects investigations and enforcement. At the same time, the government cannot be allowed to summarily act to shut down businesses without apprising the regulated industry of the rules which the government will use.

CONCLUSION

The district court erred in denying plaintiff-appellant Cardinal Health's motion for preliminary injunction and that judgment should be reversed.

Appendix not available.

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COMPLAINT

EXHIBIT #7

MMWR Vital Signs

July 4, 2014

Morbidity and Mortality Weekly Report

Vital Signs: Variation Among States in Prescribing of Opioid Pain Relievers and Benzodiazepines — United States, 2012

Leonard J. Paulozzi, MD[1], Karin A. Mack, PhD[2], Jason M. Hockenberry, PhD[3] (Author affiliations at end of text)

On July 1, 2014, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

Abstract

Background: Overprescribing of opioid pain relievers (OPR) can result in multiple adverse health outcomes, including fatal overdoses. Interstate variation in rates of prescribing OPR and other prescription drugs prone to abuse, such as benzodiazepines, might indicate areas where prescribing patterns need further evaluation.

Methods: CDC analyzed a commercial database (IMS Health) to assess the potential for improved prescribing of OPR and other drugs. CDC calculated state rates and measures of variation for OPR, long-acting/extended-release (LA/ER) OPR, high-dose OPR, and benzodiazepines.

Results: In 2012, prescribers wrote 82.5 OPR and 37.6 benzodiazepine prescriptions per 100 persons in the United States. State rates varied 2.7-fold for OPR and 3.7-fold for benzodiazepines. For both OPR and benzodiazepines, rates were higher in the South census region, and three Southern states were two or more standard deviations above the mean. Rates for LA/ER and high-dose OPR were highest in the Northeast. Rates varied 22-fold for one type of OPR, oxymorphone.

Conclusions: Factors accounting for the regional variation are unknown. Such wide variations are unlikely to be attributable to underlying differences in the health status of the population. High rates indicate the need to identify prescribing practices that might not appropriately balance pain relief and patient safety.

Implications for Public Health: State policy makers might reduce the harms associated with abuse of prescription drugs by implementing changes that will make the prescribing of these drugs more cautious and more consistent with clinical recommendations.

Introduction

Persons in the United States consume opioid pain relievers (OPR) at a greater rate than any other nation. They consume twice as much per capita as the second ranking nation, Canada (*1*). Overprescribing of opioid pain relievers can result in multiple adverse health outcomes, including fatal overdoses (*2*). Opioid pain relievers were involved in 16,917 overdose deaths in 2011; in 31% of these deaths, benzodiazepine sedatives were also cited as contributing causes (CDC WONDER, unpublished data, 2014). High rates of prescribing these controlled substances are important determinants of rates of fatal overdose and drug abuse (*3,4*). Overall state prescribing rates of OPR vary widely (*5*). Variation in prescribing rates for higher-risk opioid prescriptions (e.g., those for long-acting or extended-release [LA/ER] formulations) or those for high daily dosage have not been examined. LA/ER OPR are more prone to abuse, and high-dose formulations are more likely to result in overdoses, so they deserve special attention. Benzodiazepines are commonly prescribed in combination with OPR, even though this combination increases the risk for overdose (*6*). Interstate variation in prescribing rates for benzodiazepines has not been measured.

Information on local prescribing rates can alert authorities to atypical use and can prompt action. Such authorities include state and local health departments, law enforcement agencies, health-care systems, and licensure boards. States have the authority to track prescribing and dispensing and regulate medical practice within their borders. They can influence the rate of prescribing of controlled prescription drugs by various measures. These include passing regulations related to use of state prescription drug monitoring programs and the operation of pain clinics.

Methods

Data on prescribing in 2012 come from IMS Health's National Prescription Audit (NPA). NPA provides estimates of the numbers of prescriptions dispensed in each state based on a sample of approximately 57,000 pharmacies, which dispense nearly 80% of the retail prescriptions in the United States. Prescriptions, including refills, dispensed at retail pharmacies

and paid for by commercial insurance, Medicaid, Medicare, or cash were included.*

CDC used the numbers of prescriptions and census denominators to calculate prescribing rates for OPR, subtypes of OPR, and benzodiazepines. The OPR category included semisynthetic opioids, such as oxycodone and hydrocodone, and synthetic opioids, such as tramadol. It did not include buprenorphine products used primarily for substance abuse treatment rather than pain, methadone distributed through substance abuse treatment programs, or cough and cold formulations containing opioids. LA/ER OPR were defined as those that should be taken only 2 to 3 times a day, such as methadone, OxyContin, and Opana ER. High-dose OPR were defined as the largest formulations available for each type of OPR that resulted in a total daily dosage of ≥100 morphine milligram equivalents when taken at the usual frequency, for example, every 4–6 hours. Benzodiazepines included alprazolam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, oxazepam, quazepam, temazepam, and triazolam.

CDC calculated prescribing rates per 100 persons for the United States, each census region, and each state. CDC described the distribution of state rates using mean, standard deviation (SD), coefficient of variation (CV) (SD divided by the mean), the interquartile ratio (IQ) (75th percentile rate divided by the 25th percentile rate), and the ratio of the highest/lowest rates. Rates were transformed into multiples of the SD above or below the mean state rate of each drug.

Results

Prescribers wrote 82.5 OPR prescriptions and 37.6 benzodiazepine prescriptions per 100 persons in the United States in 2012 (Table). LA/ER OPR accounted for 12.5%, and high-dose OPR accounted for 5.1% of the estimated 258.9 million OPR prescriptions written nationwide. Prescribing rates varied widely by state for all drug types. For all OPR combined, the prescribing rate in Alabama was 2.7 times the rate in Hawaii. The high/low ratio was greater for LA/ER OPR and high-dose OPR compared with all OPR together: for high-dose OPR, state rates ranged 4.6-fold (Delaware versus Texas), and for LA/ER OPR, state rates ranged 5.3-fold (Maine versus Texas). State rates ranged 3.7-fold (West Virginia versus Hawaii) for benzodiazepines. For both OPR and benzodiazepines, Alabama, Tennessee, and West Virginia were the three highest-prescribing states. Among the OPR drugs, interstate variation was greatest for oxymorphone (CV = 0.72, IQ = 2.50, high/low = 21.9). OPR prescribing rates correlated with benzodiazepine prescribing rates ($r = 0.80$; $p<0.01$).

The distribution of state prescribing rates was skewed toward higher rates (Figure 1). For both OPR and benzodiazepine rates, Alabama, Tennessee, and West Virginia were ≥2 SDs above the mean. For LA/ER opioids, Maine and Delaware were ≥2 SDs above the mean. For high-dose OPR, Delaware, Tennessee, and Nevada were ≥2 SDs above the mean. Texas's rate for LA/ER OPR was the only rate ≥2 SDs below the mean for any category.

The South region had the highest rate of prescribing OPR and benzodiazepines (Figure 2). The Northeast had the highest rate for high-dose OPR and LA/ER OPR, although high rates also were observed in individual states in the South and West. In the Northeast, 17.8% of OPR prescribed were LA/ER OPR. States in the South ranked highest for all individual opioids except for hydromorphone, fentanyl, and methadone, for which the highest rates were in Vermont, North Dakota, and Oregon, respectively.

Conclusions and Comment

The rates of use of pain relievers and benzodiazepine sedatives showed about three- to five-fold variation from the highest to lowest states. Variation was greater for the LA/ER and high-dose formulations of OPR. Higher OPR and benzodiazepine prescribing rates in the South presented in this report are similar to the findings of higher prescribing rates for other drugs in the South, including antibiotics (*7*), stimulants in children (*8*), and medications that are high-risk for the elderly (*9*). Previous studies have found that regional prescribing variation cannot be explained by variation in the prevalence of the conditions treated by these drugs (*5,7*). Other research indicates that wide variation in rates of surgery and hospitalization also cannot be explained by the underlying health status of the population (*9,10*). Wide variation in the use of medical technology, including pharmacotherapy, usually indicates a lack of consensus on the appropriateness of its use (*9*). Therefore, one possible explanation for the results of this study is the lack of consensus among health-care providers on whether and how to use OPR for chronic, noncancer pain (*2*).

Research on small-area variation in health care indicates that high rates of use of prescription drugs and medical procedures do not necessarily translate into better outcomes or greater patient satisfaction. In fact, high rates of use might produce worse outcomes (*11,12*). In this case, greater use of opioids and benzodiazepines might expose populations to greater risks for overdose and falls (*2,3,13,14*). Greater use is also associated with abuse (*4*), although such use might both cause and be caused by abuse. The wide variation in rates of use for LA/ER

* Additional information available at http://www.imshealth.com/deployedfiles/ims/global/content/insights/researchers/npa_data_brief.pdf.

TABLE. Prescribing rates per 100 persons, by state and drug type — IMS Health, United States, 2012

State	Opioid pain relievers	Rank	Long-acting/ extended-release opioid pain relievers	Rank	High-dose opioid pain relievers	Rank	Benzodiazepines	Rank
Alabama	142.9	1	12.4	22	6.8	4	61.9	2
Alaska	65.1	46	10.7	31	4.2	26	24.0	50
Arizona	82.4	26	14.5	12	5.5	12	34.3	33
Arkansas	115.8	8	9.6	37	4.1	29	50.8	8
California	57.0	50	5.8	49	3.0	42	25.4	47
Colorado	71.2	40	11.8	24	4.1	31	28.0	44
Connecticut	72.4	38	14.1	13	5.4	13	46.2	11
Delaware	90.8	17	21.7	2	8.8	1	41.5	19
District of Columbia	85.7	23	13.7	17	5.7	10	38.4	24
Florida	72.7	37	11.3	26	6.6	5	46.9	10
Georgia	90.7	18	8.6	43	4.1	30	37.0	27
Hawaii	52.0	51	8.8	42	3.9	36	19.3	51
Idaho	85.6	24	10.3	33	3.9	34	29.1	42
Illinois	67.9	43	5.2	50	2.0	50	34.2	34
Indiana	109.1	9	10.7	30	4.9	20	42.9	17
Iowa	72.8	36	7.3	47	2.2	48	37.3	26
Kansas	93.8	16	10.3	34	4.0	32	38.9	23
Kentucky	128.4	4	11.6	25	5.0	19	57.4	5
Louisiana	118.0	7	7.8	46	3.6	39	51.5	7
Maine	85.1	25	21.8	1	5.6	11	40.7	22
Maryland	74.3	33	16.0	6	5.0	18	29.9	40
Massachusetts	70.8	41	14.9	8	3.5	41	48.8	9
Michigan	107.0	10	9.1	40	4.5	22	45.5	14
Minnesota	61.6	48	10.2	35	2.2	49	24.9	48
Mississippi	120.3	6	7.2	48	2.9	43	46.2	12
Missouri	94.8	14	9.5	38	3.5	40	42.6	18
Montana	82.0	27	14.0	15	4.4	23	33.7	35
Nebraska	79.4	28	7.8	45	2.3	46	35.0	32
Nevada	94.1	15	14.8	10	8.2	3	37.5	25
New Hampshire	71.7	39	19.6	3	6.1	7	41.2	21
New Jersey	62.9	47	11.3	27	5.8	9	36.5	28
New Mexico	73.8	35	12.7	21	3.8	38	31.5	37
New York	59.5	49	9.5	39	4.3	24	27.3	45
North Carolina	96.6	13	13.7	18	4.3	25	45.3	15
North Dakota	74.7	32	10.5	32	2.3	47	31.1	39
Ohio	100.1	12	11.2	28	4.2	27	41.3	20
Oklahoma	127.8	5	12.8	20	6.0	8	44.5	16
Oregon	89.2	20	18.8	4	5.2	16	31.4	38

opioids, in particular, might reflect the demand for these drugs in the drug-using community and their selective prescribing, often in combination with sedatives and muscle relaxants, by unscrupulous pain clinics (*14*). Factors that might explain why some states have consistently lower rates of prescribing also need to be identified in future research.

The findings in this report are subject to at least four limitations. First, IMS estimates have not been validated, and they do not include prescriptions dispensed by prescribers, hospital/clinic pharmacies, or health maintenance organization pharmacies, potentially biasing rates downward. Second, prescriptions might be dispensed to nonstate residents, as commonly occurred in Florida during the previous decade (*14*). Third, prescribing rates cannot be correlated with rates of outcomes, such as overdoses with these drugs, because drug-specific overdose data are not available for most jurisdictions. Finally, the prescribing rates shown for a state might conceal large differences in rates within the state (*15*).

Evaluating and modifying state prescribing patterns is particularly important in states with the highest prescribing rates for drugs prone to abuse. States can determine the factors driving their high prescribing rates by using data from their prescription drug monitoring programs (PDMPs), systems that record all prescriptions for drugs prone to abuse. They can also use PDMPs to evaluate the impacts of policy changes. Recently, a few states have been able to change prescribing patterns by increasing prescriber use of their PDMPs. New York and Tennessee, for example, mandated prescriber use of the state PDMP in 2012. They subsequently used their PDMPs to document declines of 75% and 36%, respectively, in the inappropriate use of multiple prescribers by patients (*16*).

TABLE. (*Continued*) Prescribing rates per 100 persons, by state and drug type — IMS Health, United States, 2012

State	Opioid pain relievers	Rank	Long-acting/ extended-release opioid pain relievers	Rank	High-dose opioid pain relievers	Rank	Benzodiazepines	Rank
Pennsylvania	88.2	21	14.9	9	5.4	14	46.1	13
Rhode Island	89.6	19	14.0	14	5.2	17	60.2	4
South Carolina	101.8	11	11.0	29	3.9	33	52.6	6
South Dakota	66.5	45	9.0	41	2.5	45	28.0	43
Tennessee	142.8	2	18.2	5	8.7	2	61.4	3
Texas	74.3	34	4.2	51	1.9	51	29.8	41
Utah	85.8	22	12.1	23	5.3	15	35.9	30
Vermont	67.4	44	13.9	16	4.7	21	35.5	31
Virginia	77.5	29	9.9	36	3.8	37	36.4	29
Washington	77.3	30	14.6	11	4.1	28	27.1	46
West Virginia	137.6	3	15.7	7	6.2	6	71.9	1
Wisconsin	76.1	31	13.1	19	3.9	35	33.4	36
Wyoming	69.6	42	8.0	44	2.7	44	24.1	49
Mean	*87.3*	—	*12.0*	—	*4.5*	—	*39.2*	—
Standard deviation	*22.4*	—	*3.9*	—	*1.6*	—	*11.1*	—
Coefficient of variation	*0.26*	—	*0.32*	—	*0.36*	—	*0.28*	—
Median	*82.4*	—	*11.3*	—	*4.2*	—	*37.3*	—
25th percentile	*71.7*	—	*9.5*	—	*3.7*	—	*31.1*	—
75th percentile	*96.6*	—	*14.1*	—	*5.4*	—	*46.1*	—
Interquartile ratio	*1.3*	—	*1.5*	—	*1.4*	—	*1.5*	—
Ratio of highest to lowest	*2.7*	—	*5.3*	—	*4.6*	—	*3.7*	—
Northeast	70.8		12.6		4.8		38.2	
South	93.7		10.2		4.6		43.1	
Midwest	88.4		9.3		3.4		38.1	
West	68.0		9.6		3.9		27.9	
U.S. rate	82.5	—	10.3	—	4.2	—	37.6	—

Key Points

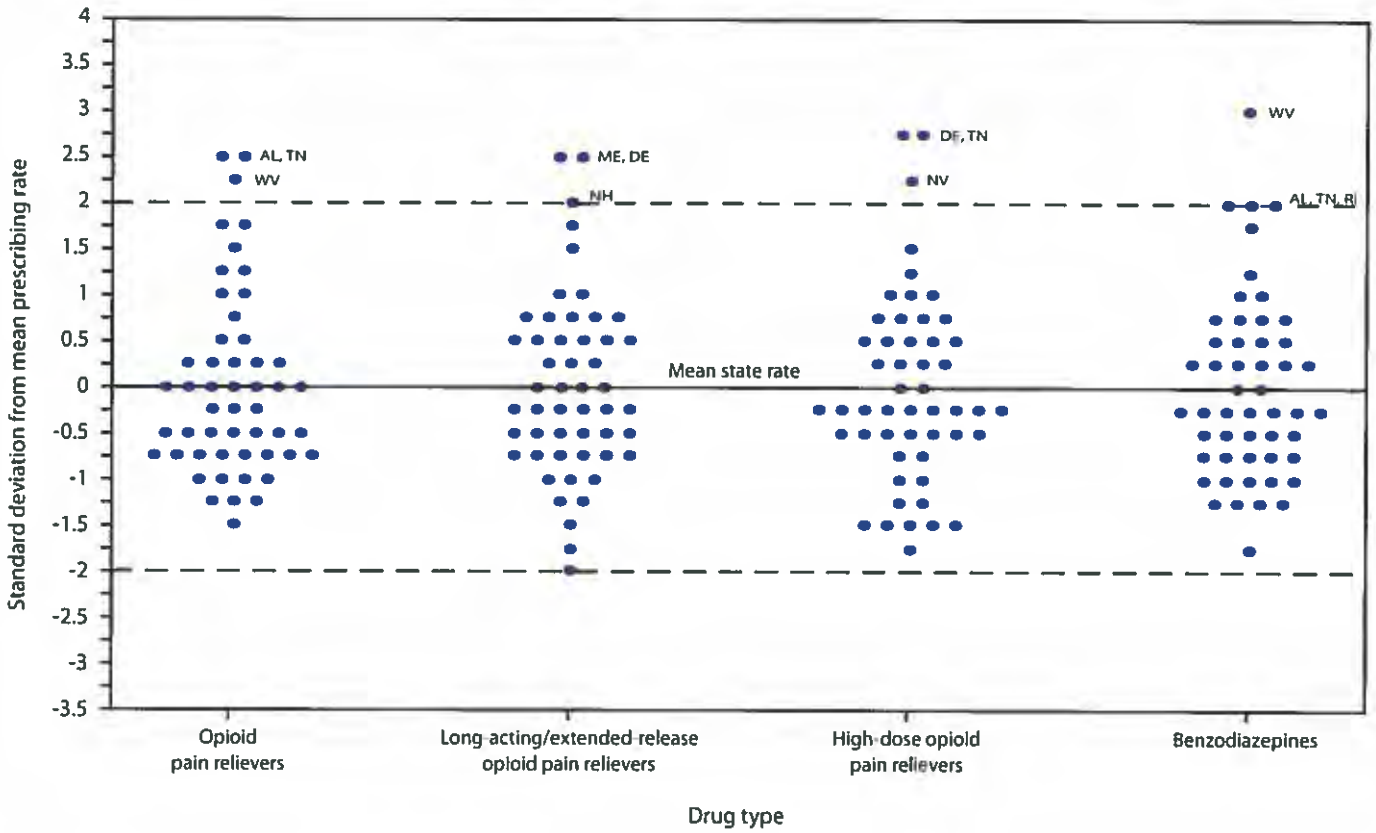
- Opioid pain relievers and benzodiazepine sedatives are commonly prescribed in the United States. They are frequently prescribed to the same patient.
- Overprescribing of opioid pain relievers can result in multiple adverse health outcomes, including fatal overdoses.
- Wide variation exists from one state to another in prescribing rates for these drugs. For states that prescribe well above the national rate, the need for a change in prescribing practices is urgent.
- CDC recommends that states make active use of their prescription drug monitoring programs to calculate current rates of prescribing, examine variations within the state, and track the impact of safer prescribing initiatives.
- Additional information is available at http://www.cdc.gov/vitalsigns.

States can take other actions that will affect prescribers. Developing or adopting existing guidelines for prescribing OPR and other controlled substances can establish local standards of care that might help bring prescribing rates more in line with current best practices. State Medicaid programs can manage pharmacy benefits so as to promote cautious, consistent use of OPR and benzodiazepines. In addition, a number of states have passed laws designed to address the most egregious prescribing excesses. Florida, for example, enacted pain clinic legislation in 2010 and prohibited dispensing by prescribers in 2011. It subsequently experienced a decline in rates of drug diversion (*17*) and a 52% decline in its oxycodone overdose death rate (*18*). Guidelines, insurance strategies, and laws are promising interventions that need further evaluation. Patients in all states deserve access to safe and effective evidence-based medical care, and prescribers should carefully consider the balance between risks and benefits in any pharmacotherapy.

Acknowledgments

Rose Rudd, MSPH, National Center for Injury Prevention and Control, CDC. Caitlin Koris, Rollins School of Public Health, Emory University.

FIGURE 1. Distribution of state prescribing rates,* by drug type — IMS Health, United States, 2012



* State rates are rounded to the nearest 0.25 standard deviation for purposes of presentation.

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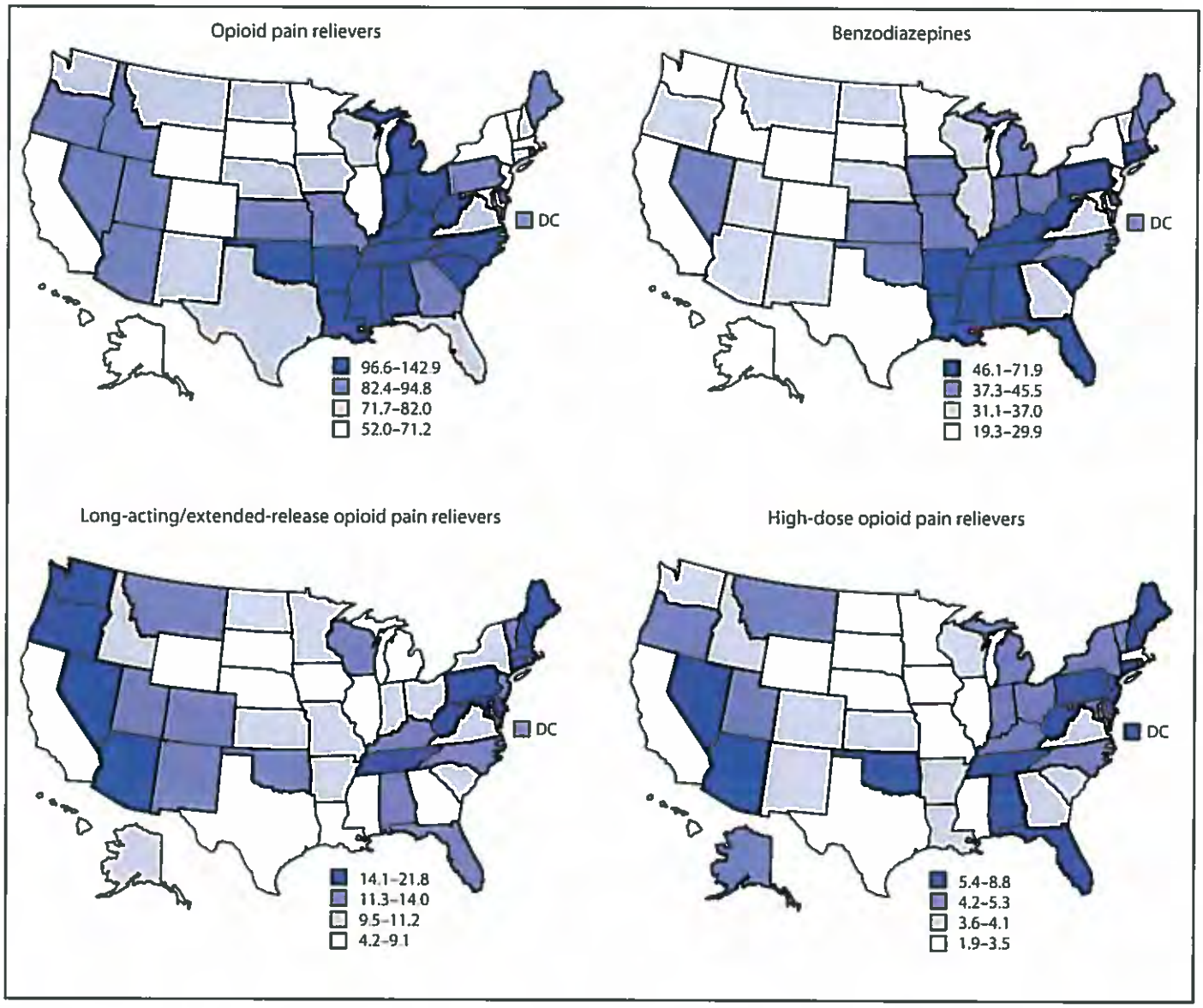
FIGURE 2. Prescribing rates per 100 persons (in quartiles), by state and drug type — IMS Health, United States, 2012



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COMPLAINT

EXHIBIT #8

CDC Vital Signs

July 2015

JULY 2015

CDC Vitalsigns™

Today's Heroin Epidemic

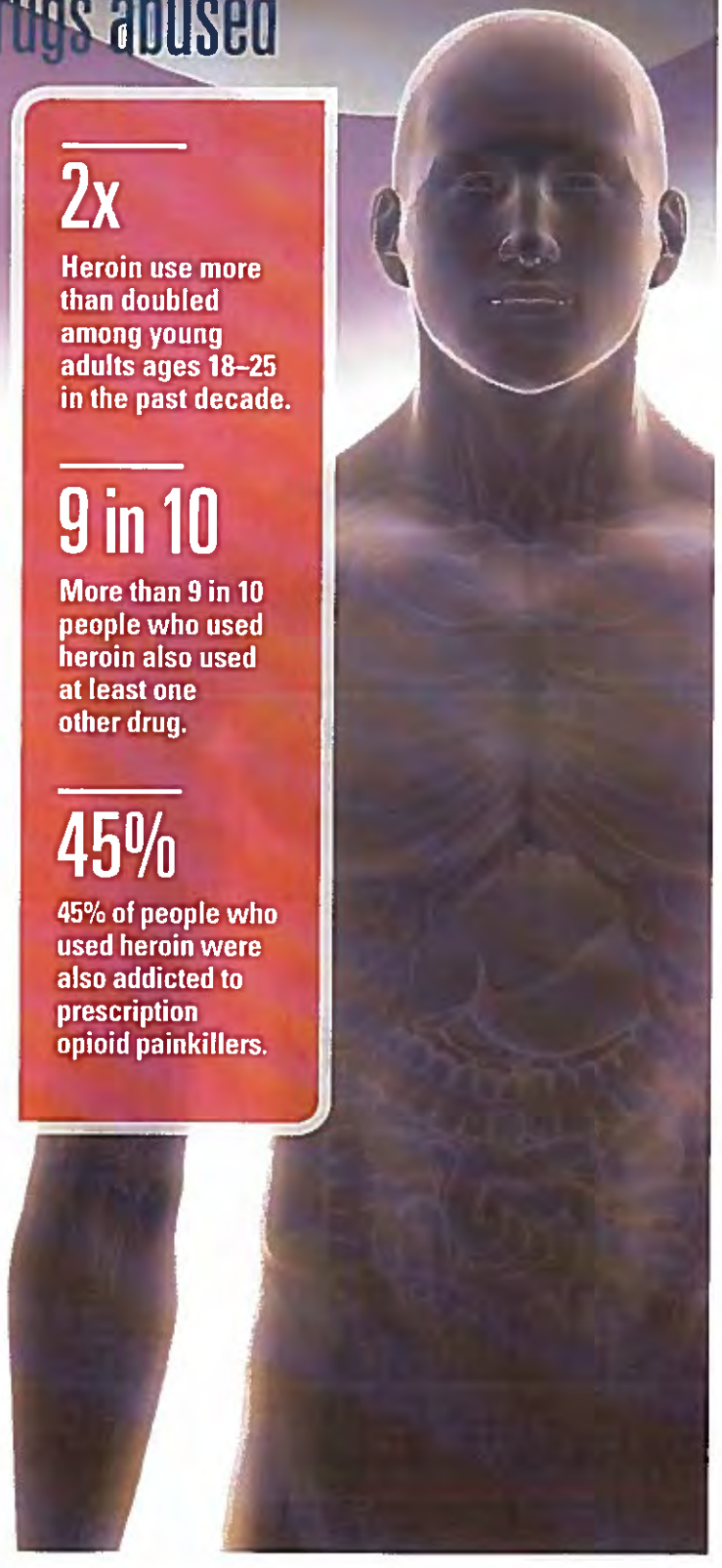
More people at risk, multiple drugs abused

Heroin use has increased across the US among men and women, most age groups, and all income levels. Some of the greatest increases occurred in demographic groups with historically low rates of heroin use: women, the privately insured, and people with higher incomes. Not only are people using heroin, they are also abusing multiple other substances, especially cocaine and prescription opioid painkillers. As heroin use has increased, so have heroin-related overdose deaths. Between 2002 and 2013, the rate of heroin-related overdose deaths nearly quadrupled, and more than 8,200 people died in 2013. States play a central role in prevention, treatment, and recovery efforts for this growing epidemic.

States can:

- Address the strongest risk factor for heroin addiction: addiction to prescription opioid painkillers.
- Increase access to substance abuse treatment services, including Medication-Assisted Treatment (MAT), for opioid addiction.
- Expand access to and training for administering naloxone to reduce opioid overdose deaths.
- Ensure that people have access to integrated prevention services, including access to sterile injection equipment from a reliable source, as allowed by local policy.
- Help local jurisdictions to put these effective practices to work in communities where drug addiction is common.

Want to learn more? www.cdc.gov/vitalsigns/heroin



2x

Heroin use more than doubled among young adults ages 18–25 in the past decade.

9 in 10

More than 9 in 10 people who used heroin also used at least one other drug.

45%

45% of people who used heroin were also addicted to prescription opioid painkillers.

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

Problem:

Heroin use is increasing, and so are heroin-related overdose deaths.

How is heroin harmful?

- Heroin is an illegal, highly addictive opioid drug.
- A heroin overdose can cause slow and shallow breathing, coma, and death.
- People often use heroin along with other drugs or alcohol. This practice is especially dangerous because it increases the risk of overdose.
- Heroin is typically injected but is also smoked or snorted. When people inject heroin, they are at risk of serious, long-term viral infections such as HIV, Hepatitis C, and Hepatitis B, as well as bacterial infections of the skin, bloodstream, and heart.

Who is most at risk of heroin addiction?

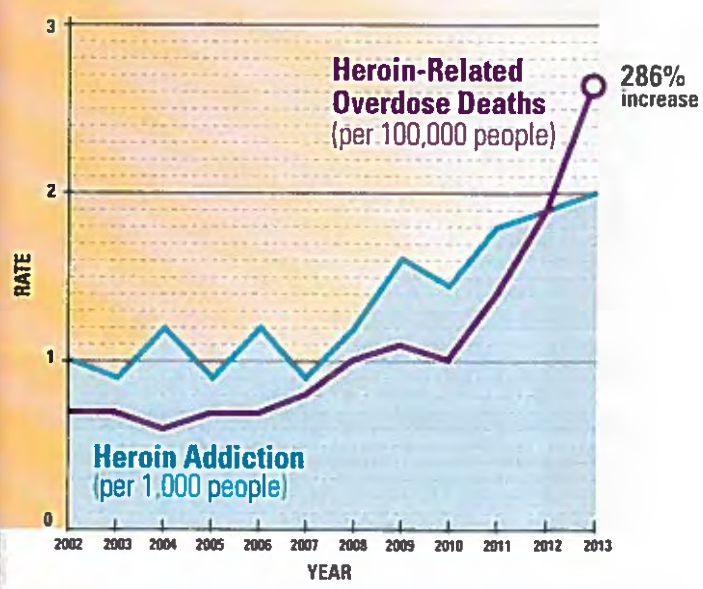
- People who are addicted to prescription opioid painkillers
- People who are addicted to cocaine
- People without insurance or enrolled in Medicaid
- Non-Hispanic whites
- Males
- People who are addicted to marijuana and alcohol
- People living in a large metropolitan area
- 18 to 25 year olds

Heroin Use Has INCREASED Among Most Demographic Groups

	2002-2004*	2011-2013*	% CHANGE
SEX			
Male	2.4	3.6	50%
Female	0.8	1.6	100%
AGE, YEARS			
12-17	1.8	1.6	--
18-25	3.5	7.3	109%
26 or older	1.2	1.9	58%
RACE/ETHNICITY			
Non-Hispanic white	1.4	3	114%
Other	2	1.7	--
ANNUAL HOUSEHOLD INCOME			
Less than $20,000	3.4	5.5	62%
$20,000–$49,999	1.3	2.3	77%
$50,000 or more	1	1.6	60%
HEALTH INSURANCE COVERAGE			
None	4.2	6.7	60%
Medicaid	4.3	4.7	--
Private or other	0.8	1.3	63%

*Annual average rate of heroin use (per 1,000 people in each group)

Heroin Addiction and Overdose Deaths are Climbing



SOURCES National Survey on Drug Use and Health (NSDUH), 2002-2013
National Vital Statistics System, 2002-2013

Heroin use is part of a larger substance abuse problem.

Nearly all people who used heroin also used at least 1 other drug.

Most used at least 3 other drugs.

Heroin is a highly addictive opioid drug with a high risk of overdose and **death** for users.

People who are addicted to...

ALCOHOL are **2x**

MARIJUANA are **3x**

COCAINE are **15x**

Rx OPIOID PAINKILLERS are **40x**

...more likely to be addicted to heroin.

SOURCE: National Survey on Drug Use and Health (NSDUH), 2011-2013

Responding to the Heroin Epidemic

PREVENT People From Starting Heroin

Reduce prescription opioid painkiller abuse.
Improve opioid painkiller prescribing practices and identify high-risk individuals early.

REDUCE Heroin Addiction

Ensure access to Medication-Assisted Treatment (MAT).
Treat people addicted to heroin or prescription opioid painkillers with MAT which combines the use of medications (methadone, buprenorphine, or naltrexone) with counseling and behavioral therapies.

REVERSE Heroin Overdose

Expand the use of naloxone.
Use naloxone, a life-saving drug that can reverse the effects of an opioid overdose when administered in time.

SOURCE: CDC Vitalsigns, July 2015

What Can Be Done?

The Federal government is

- Providing educational training and resources to health care providers so they can make informed decisions and ensure the appropriate prescribing of opioid painkillers. This includes:
  - Developing prescribing guidelines for chronic pain.
  - Supporting the use of prescription drug monitoring programs (electronic databases that track the dispensing of certain drugs) as a routine part of clinical practice.
- Increasing access to substance abuse treatment services through the Affordable Care Act.
- Expanding use of Medication-Assisted Treatment (MAT).
- Supporting the development and distribution of the life-saving drug naloxone to reduce prescription opioid painkiller and heroin overdose deaths.
- Supporting the research, development, and approval of pain medications that are less prone to abuse.
- Improving surveillance to better track trends, identify communities at risk, and target prevention strategies.

States can

- Address the strongest risk factor for heroin addiction: addiction to prescription opioid painkillers.
  - Make prescription drug monitoring programs timely and easy to use. Providers can analyze patient prescription drug history and make informed decisions before prescribing opioid painkillers.
  - Look at the data and practices of state Medicaid and worker's compensation programs to identify and reduce inappropriate prescribing.
- Increase access to substance abuse treatment services, including MAT for opioid addiction.
  - Work with Medicaid and other insurance companies to provide coverage for MAT.
  - Support adoption of MAT in community settings.
- Expand access to and training for administering naloxone to reduce opioid overdose deaths.
- Ensure that people have access to integrated prevention services, including access to sterile injection equipment from a reliable source, as allowed by local policy.
- Help local jurisdictions to put these effective practices to work in communities where drug addiction is common.

Health care providers can

- Follow best practices for responsible painkiller prescribing to reduce opioid painkiller addiction, the strongest risk factor for heroin addiction:
  - Use prescription drug monitoring programs and ask patients about past or current drug and alcohol use prior to considering opioid treatment.
  - Prescribe the lowest effective dose and only the quantity needed for each patient.
  - Link patients with substance use disorders to effective substance abuse treatment services.
- Support the use of Food and Drug Administration-approved MAT options (methadone, buprenorphine, and naltrexone) in patients addicted to prescription opioid painkillers or heroin.

Everyone can

Learn more about the risks of using heroin and other drugs.

- Learn how to recognize and respond to an opioid overdose.
- Get help for substance abuse problems: **1-800-662-HELP**.

For more information on MAT and naloxone, visit SAMHSA at: www.samhsa.gov.

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COMPLAINT

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Relationship between Nonmedical Prescription-Opioid Use and Heroin Use

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THE NONMEDICAL USE OF PRESCRIPTION OPIOIDS IS A MAJOR PUBLIC health issue in the United States, both because of the overall high prevalence and because of marked increases in associated morbidity and mortality.[1] In 2014, a total of 10.3 million persons reported using prescription opioids nonmedically (i.e., using medications that were not prescribed for them or were taken only for the experience or feeling that they caused).[2] Emergency department visits involving misuse or abuse of prescription opioids increased 153% between 2004 and 2011, and admissions to substance-abuse treatment programs linked to prescription opioids more than quadrupled between 2002 and 2012.[3,4] Most troubling, between 2000 and 2014 the rates of death from prescription-opioid overdose nearly quadrupled (from 1.5 to 5.9 deaths per 100,000 persons) (Fig. 1).

The pattern of nonmedical use of prescription opioids varies, from infrequent use once or twice per year to daily or compulsive heavy use and addiction. A key underlying characteristic of the epidemic is the association between the increasing rate of opioid prescribing and increasing opioid-related morbidity and mortality.[6-9] Pain has also been identified as a poorly addressed clinical and public health problem for which treatment with prescription opioids may play an important role.[10] Taken together, these trends suggest the need for balanced prevention responses that aim to reduce the rates of nonmedical use and overdose while maintaining access to prescription opioids when indicated.

In response to these interrelated public health problems, federal, state, and other vested interests are implementing a variety of policies and programs aimed at curbing inappropriate prescribing.[1,6,11-16] These efforts include educating health professionals and the public about appropriate use, implementing prescription-drug monitoring programs, taking enforcement and regulatory actions to address egregious prescribing (e.g., eliminating "pill mills"), and developing prescription opioids that incorporate abuse-deterrent technologies.

Although more rigorous evaluation is needed, there are some indications that these initiatives are beginning to show some success. A recent study showed that the rate of opioid prescribing in the United States stabilized between 2010 and 2012, with some medical specialties showing declines in the rate of opioid prescribing after consistent increases for a number of years.[17] States and localities that took the most decisive action are seeing a decrease in the availability of prescription opioids coupled with a decline in the rate of deaths from overdose.[13-15] Using national data, the Centers for Disease Control and Prevention reported that there were 16,007 and 16,235 overdose-related deaths in 2012 and 2013, respectively, involving opioid analgesic agents, down from a peak of 16,917 deaths in 2011; however, the 18,893 deaths reported in 2014 suggest continued concerns.[5] An-

other study showed that abuse of prescription opioids increased between 2002 and 2010 and then plateaued between 2011 and 2013.[18]

Coinciding with these efforts to reduce nonmedical prescription-opioid use and overdose are reports of increases in the rates of heroin use (including both injection and noninjection routes of administration) and deaths from heroin overdose. According to national surveillance data, 914,000 people reported heroin use in 2014, a 145% increase since 2007,[2] and mortality due to heroin overdose more than quintupled, from 1842 deaths in 2000 to 10,574 deaths in 2014.[5] Some researchers suggest that the very policies and practices that have been designed to address inappropriate prescribing are now fueling the increases in rates of heroin use and death.[16,18] This is the key question addressed in this review.

Some persons certainly use heroin when they are unable to obtain their preferred prescription opioid; however, whether the increases in heroin trends in the overall population are driven by changes in policies and practices regarding prescription opioids is much less clear. As an alternative explanation, we explore the complexity and reciprocal nature of this relationship and review the pharmacologic basis for heroin use among people who use prescription opioids nonmedically, the patterns of heroin use among people who use prescription opioids nonmedically, the current trends in heroin use and their correlates, and the effects on heroin use of policies aimed at curbing inappropriate prescribing of opioids. A clearer understanding of these relationships will help to guide clinical practice and public health interventions and avoid the error of simply shifting the problem from one drug to another.

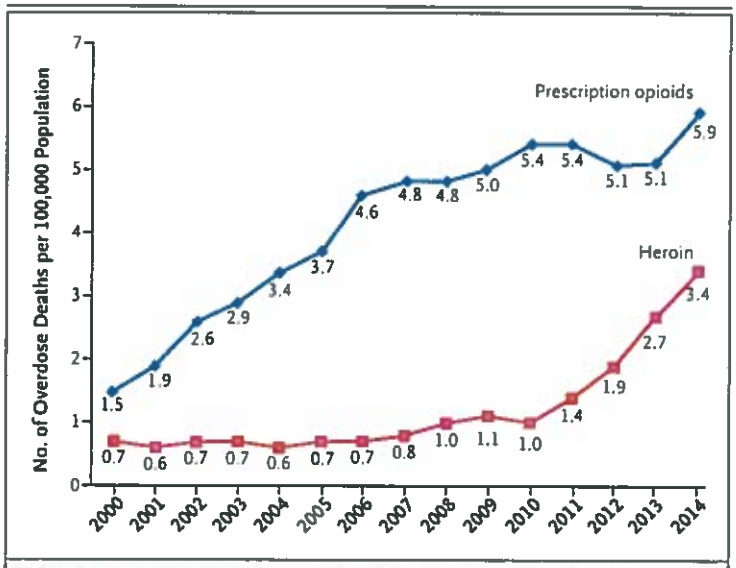

Figure 1. Age-Adjusted Rates of Death Related to Prescription Opioids and Heroin Drug Poisoning in the United States, 2000–2014.

Data are from the Centers for Disease Control and Prevention.[5]

PHARMACOLOGIC SIMILARITIES OF HEROIN AND PRESCRIPTION OPIOIDS

Heroin is pharmacologically similar to prescription opioids. All these drugs produce their action through endogenous opioid systems that regulate a wide range of functions through three major types of G-protein–coupled receptors: mu, delta, and kappa, with particularly potent agonist activity at the mu receptor and weak activity at the delta and kappa receptors.[19,20] Mu-receptor activation by an agonist such as heroin or a prescription opioid triggers a complex cascade of intracellular signaling events, which ultimately lead to an increase in dopamine release in the shell of the nucleus accumbens.[19,20] The resulting burst of dopamine in this critical area of the reward circuitry becomes strongly coupled with the subjective "high" that is caused by drugs of abuse.[21]

The abuse liability of an opioid is determined by multiple factors, including the lipophilicity of the drug (i.e., its ability to cross the blood–brain barrier rapidly), its binding affinity for the mu receptor, and various pharmacokinetic and physicochemical characteristics (e.g., the ease with which it can be abused by means of injection and insufflation routes of administration).[22,23] Thus, although prescription opioids and heroin both have the potential to use similar pharmacologic mechanisms to induce euphoria (or analgesia), different opioid molecules have different euphorigenic properties and withdrawal-syndrome patterns.

These factors could also influence the potential for abuse of the various opioid drugs, because opioid drug–taking behavior is likely to be influenced by the balance between positive and negative subjective ratings engendered by a specific opioid. For example, a study involving heroin abusers showed that the reinforcing effects of oxycodone were similar to those produced by

morphine or heroin, but unlike morphine or heroin, oxycodone produced no "bad" effects in the participants in the study.[23] Similar considerations may help explain why several prescription opioids — such as hydromorphone, fentanyl, morphine, and oxycodone — have a potential for abuse that is similar to, and in some cases even higher than, the potential for abuse with heroin.[22,23] Finally, these differential properties and effects are likely to interact with interindividual variability in powerful, complex, and incompletely predictable ways, so that some persons who abuse prescription opioids could find heroin less rewarding than prescription opioids, similarly rewarding, or even more rewarding.[24,25]

HEROIN USE AMONG PEOPLE WHO USE PRESCRIPTION OPIOIDS NONMEDICALLY

Studies that address the patterns of heroin use in nonmedical users of prescription opioids are mostly observational and descriptive (i.e., nonexperimental). Thus, conclusions about cause and effect are uncertain. Yet, certain consistent findings of a positive association between nonmedical use of prescription opioids and heroin use are highly suggestive and plausible, given the common pharmacologic principles described above.

Using national-level data, Becker et al. found that heroin users were 3.9 times as likely to report nonmedical use of opioids in the previous year, and 2.9 times as likely to meet the criteria for abuse or dependence on opioids, as persons who did not use heroin.[26] Grau et al. found that nonmedical use of multiple opioids was associated with transitioning to heroin.[27] Similarly, Muhuri et al. found that the incidence of heroin use among people who reported prior nonmedical use of prescription opioids was 19 times as high as the incidence among persons who reported no previous nonmedical use.[28] Additional studies involving persons from various geographic, economic, and drug-using backgrounds have shown similar associations.[29-33]

A limited number of small studies examined the sequence of and trajectories from nonmedical use of prescription opioids to heroin use. In 2003, Siegal et al. were among the first to suggest the pathway from nonmedical use of opioids to heroin use.[34] They found that in Ohio, 50% of persons 18 to 33 years of age who had recently begun using heroin reported having abused opioids, primarily OxyContin, before initiating heroin use.[34] A larger study involving young urban people who used injected heroin in New York and Los Angeles in 2008 and 2009 showed that 86% had used opioids nonmedically before using heroin.[35] Similar studies conducted in San Diego, Seattle, and New York showed that 40%, 39%, and 70% of heroin users, respectively, reported that they had used prescription opioids nonmedically before initiating heroin use.[36-38]

Trajectory analysis of patterns of nonmedical use of prescription opioids suggests that persons most often start with oral nonmedical use of opioids. They move to more efficient routes of administration, such as insufflation, smoking, or injection, as tolerance to opioids develops and it becomes more costly to maintain their abuse patterns. By the time they initiate heroin use, usually through contact with drug users, sexual partners, or drug dealers, they view heroin as reliably available, more potent, easier to manipulate for nonoral routes, and more cost-effective than prescription opioids.[34-36,38-41]

In an effort to examine whether the findings from these small studies were consistent with findings in the broader population of nonmedical users, the sequence regarding initiation of use was assessed with the use of both treatment-population data and general-population data. Among heroin users entering substance-abuse treatment programs, Cicero et al. found significant shifts in the pattern of the first opioid used by those with recent onset as compared with those started using opioids 40 to 50 years ago.[41] Among persons who began their opioid use in the 1960s, more than 80% reported that their first opioid was heroin; conversely, in the 2000s, a total of 75% of users initiated opioid use with prescription opioids.[41]

Using national-level, general-population data, Jones found that in the period from 2008 through 2010, among people who used both prescription opioids for nonmedical reasons and heroin during the previous year, 77.4% reported using prescription opioids before initiating heroin use.[42] Similarly, Muhuri and colleagues found that 79.5% of persons who recently began using heroin had used prescription opioids nonmedically before initiating heroin use.[28] Both studies showed that heroin use was most common among persons who were frequent users of

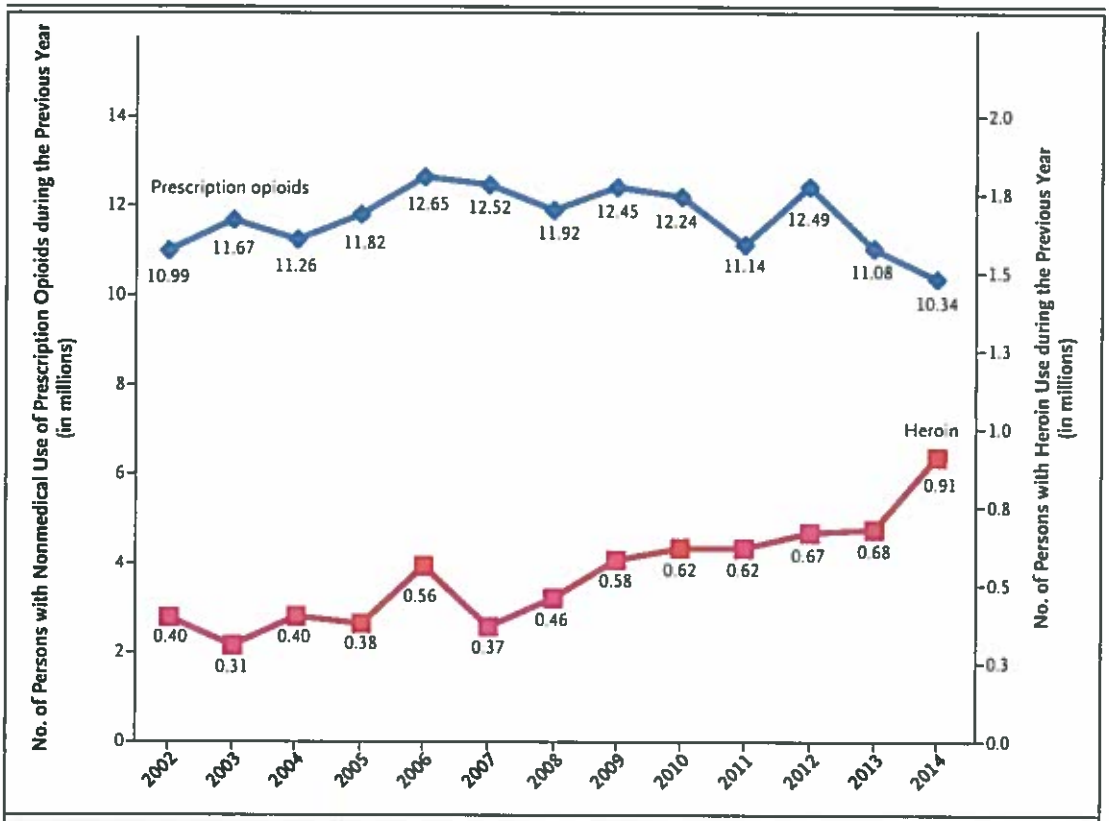

Figure 2. Nonmedical Use of Prescription Opioids and Heroin during the Previous Year among Noninstitutionalized Persons 12 Years of Age or Older, 2002–2014.

Data are from the Center for Behavioral Health Statistics and Quality.[2]

nonmedical opioids.[28,42] A recent study with data through 2013 showed that prescription-opioid abuse or dependence was associated with a likelihood of heroin abuse or dependence that was 40 times as great as the likelihood with no prescription-opioid abuse or dependence, even after accounting for sociodemographic, geographic, and other substance abuse or dependence characteristics.[43] These studies suggest a clear link between nonmedical use of prescription opioids and heroin use, especially among persons with frequent nonmedical use or those with prescription-opioid abuse or dependence.

CURRENT TRENDS IN HEROIN USE AND THEIR CORRELATES

Heroin use has been increasing in the United States for the past 10 years, especially since 2007 (Fig. 2), an increase that has occurred in the context of broad use of multiple substances.[43] As seen in Table 1, in addition to the 138.9% increase in heroin use among nonmedical users of prescription opioids between the period of 2002–2004 and the period of 2011–2013, heroin use increased 97.5% among nonmedical users of other prescription drugs (stimulants, tranquilizers, and sedatives), 87.3% among users of cocaine, 57.3% among people who binge drink, and 45.4% among marijuana users.[43] Moreover, heroin users increasingly report abuse of or dependence on other substances.[43] There have also been shifts in the demographic characteristics associated with heroin use; the rate has increased particularly steeply among persons 18 to 25 years of age, and increases have been observed in both large urban areas and other geographic regions, in both sexes but more among women than among men, and in all races and ethnic groups but more among non-Hispanic whites than among others.[43]

Table 2 shows the sociodemographic, geographic, and substance-use groups that are associated with the greatest risk of heroin abuse or dependence during the previous year in the period of 2011–2013.[43] Other studies have shown

Table 1. Annual Average Rates of Heroin Use during the Previous Year, According to Substance-Use Characteristic and Time Period, in the United States, 2002–2013.*

Characteristic	2002–2004		2005–2007		2008–2010		2011–2013	Percent Change		P Value†
	Rate (95% CI)	P Value	Rate (95% CI)	P Value	Rate (95% CI)	P Value	Rate (95% CI)	2008–2010 to 2011–2013	2002–2004 to 2011–2013	
								percent		
Binge drinking during previous month	3.7 (3.0–4.5)	0.001	4.1 (3.3–5.1)	0.02	5.2 (4.3–6.3)	0.38	5.8 (4.4–6.4)	12.30	57.3	0.006
Marijuana use during previous year	11.6 (9.5–14.1)	0.004	13.2 (10.6–16.4)	0.07	14.4 (12.6–16.6)	0.16	16.9 (14.4–19.8)	16.70	45.4†	0.004
Cocaine use during previous year	48.9 (40.2–59.3)	<0.001	57.6 (45.9–72.2)	<0.001	68.3 (55.4–83.9)	0.02	91.5 (78.2–106.8)	34.00	87.3†	<0.001
Nonmedical use of prescription opioid during previous year	17.8 (14.3–22.0)	<0.001	25.1 (19.9–31.7)	<0.001	34.0 (28.9–39.8)	0.048	42.4 (36.6–49.1)	24.80	138.9†	<0.001
Nonmedical use of other psychotherapeutic agent during previous year‡	23.1 (18.6–28.7)	<0.001	28.5 (23.1–35.1)	<0.001	41.6 (33.8–51.0)	0.48	45.6 (38.9–53.4)	9.70	97.5†	<0.001

* Data are from Jones et al.[43] The rate is per 1000 population in each analytic group. P values are for the comparison with the rate in the period of 2011–2013.
† The P values are for trend.
‡ Other psychotherapeutic agents included tranquilizers, sedatives, and stimulants.

that recent cohorts of heroin users entering treatment have been likely to be white, middle-class, and living in nonurban areas; this result mirrors the populations that have had the largest increases in rates of nonmedical use of prescription opioids since 2002.[2,41,42,44] These findings are generally consistent with those from a number of smaller studies.[34-40]

A key factor underlying the recent increases in rates of heroin use and overdose may be the low cost and high purity of heroin.[45,46] The price in retail purchases has been lower than $600 per pure gram every year since 2001, with costs of $465 in 2012 and $552 in 2002, as compared with $1237 in 1992 and $2690 in 1982.[45] A recent study showed that each $100 decrease in the price per pure gram of heroin resulted in a 2.9% increase in the number of hospitalizations for heroin overdose.[46] In addition, regions of the United States that are not typically centers for heroin distribution or availability have seen marked increases in recent years.[47,48]

In the context of marked increases in the rates of heroin use, it is important to note that only a small percentage of nonmedical users of prescription opioids initiate heroin use. Muhuri and colleagues found that 3.6% of nonmedical users initiated heroin use within 5 years after beginning nonmedical use of prescription opioids.[28] Jones et al. found that approximately 4.2% of persons who had used prescription opioids nonmedically during the previous year in the period of 2011–2013 also reported using heroin during the previous year.[43] Of note, given the large number of nonmedical users, even a small percentage who initiate heroin use translates into several hundred thousand new heroin users. Yet, taken in total, the available data suggest that nonmedical prescription-opioid use is neither necessary nor sufficient for the initiation of heroin use and that other factors are contributing to the increase in the rate of heroin use and related mortality.

EFFECTS OF OPIOID-PRESCRIBING INTERVENTIONS ON HEROIN USE

Multiple studies that have examined why some persons who abuse prescription opioids initiate heroin use indicate that the cost and availability of heroin were primary factors in this process. These reasons were generally consistent across

time periods from the late 1990s through 2013.[34-41] Some interviewees made reference to doctors generally being less willing to prescribe opioids as well as to increased attention to the issue by law enforcement, which may have affected the available supply of opioids locally.[38,40] It should be noted that most of these studies were conducted before 2009 — a time when few policies targeting opioid prescribing were implemented.

It appears that the shift toward heroin use among some nonmedical users of prescription opioids was occurring before the recent policy focus on prescription-opioid abuse took hold. This observation is supported by data on heroin use reported to U.S. poison control centers that show increases starting in 2006,[18] as well as national surveillance data that show a rise in heroin use starting in 2007.[2] Similarly, a study examining hospitalizations for heroin overdose between 1993 and 2009 showed that the rate of such hospitalizations increased 69% between 1993 and 2006 and then rose more sharply, by 44%, between 2005 and 2009.[49] Furthermore, this study showed that these increases occurred in the context of continued increases in the rate of hospitalization for overdose of prescription opioids.

The results of the studies by Dart et al. and Cicero et al. suggest an association between the introduction of an abuse-deterrent formulation of OxyContin and increases in rates of heroin use.[16,18] Dart et al. found evidence that rates of heroin use increased after the introduction of the abuse-deterrent formulation, but they also reported that the rate of heroin use was increasing previously.[18] Cicero et al. found that a decrease in the rate of OxyContin abuse corresponded with an increase in the rate of heroin use over the 2 years after the introduction of the abuse-deterrent formulation.[16] However, in a follow-up study, Cicero and Ellis found that over the ensuing 18 months, the rates of OxyContin abuse no longer decreased whereas the rates of heroin use continued to increase.[50] Moreover, a separate study involving patients who were being screened for substance-abuse treatment showed no significant differences between the prevalence of heroin use before the introduction of the reformulation and the prevalence after the reformulated drug was available.[51]

Five recent quantitative studies provide additional insights into the relationship between opioid-prescribing policies and practices and heroin use and overdose. First was an analysis of deaths due to overdose in North Carolina be-

Table 2. Demographic and Substance-Use Characteristics Associated with Heroin Abuse or Dependence during the Previous Year in the United States, 2011–2013.*

Characteristic	Adjusted Odds Ratio (95% CI)	P Value
Sex		
Male	2.1 (1.4–3.0)	<0.001
Female	1.0	
Age group		
12–17 yr	0.3 (0.1–0.6)	0.001
18–25 yr	1.0	
≥26 yr	0.6 (0.4–0.9)	0.008
Race or ethnic group†		
Non-Hispanic white	3.1 (1.8–5.1)	<0.001
Other	1.0	
Geographic region of residence		
CBSA with ≥1 million persons	2.4 (1.5–3.6)	<0.001
Other	1.0	
Annual household income		
<$20,000	1.0	
$20,000–$49,999	0.5 (0.3–0.7)	0.001
≥$50,000	0.6 (0.3–0.9)	0.02
Insurance coverage		
No insurance	3.1 (2.2–4.3)	<0.001
Medicaid	3.2 (1.9–5.4)	<0.001
Private or other insurance	1.0	
Substance abuse or dependence in previous year		
None	1.0	
Alcohol	1.8 (1.2–2.9)	0.009
Marijuana	2.6 (1.5–4.6)	0.002
Cocaine	14.7 (7.4–29.2)	<0.001
Prescription opioid	40.0 (24.6–65.3)	<0.001
Other psychotherapeutic agent‡	1.6 (0.8–3.2)	0.22

* Odds ratios and 95% confidence intervals were calculated with the use of multivariable logistic-regression analyses. Data are from Jones et al.[43] CBSA denotes core-based statistical area.

† Race and ethnic group were based on survey respondents' self-classification of racial and ethnic origin and identification according to the classifications developed by the U.S. Census Bureau.

‡ Other psychotherapeutic agents included tranquilizers, sedatives, and stimulants.

tween 2007 and 2013, which documented a shift toward an increasing risk of death due to heroin use.[52] However, the shift began in 2009, before changes such as the introduction of abuse-deterrent formulations of opioids were in effect.[52] The second study showed that heroin-related emergency department visits, hospital admissions, and overdose deaths in Wisconsin started to increase in 2007.[53] Furthermore, these increases in rates of heroin overdose were superimposed on continued increases in rates of prescription-opioid overdoses through 2012.[53]

The third study examined deaths from overdose in Florida through 2012.[13,54] Florida had a well-documented prescription-opioid problem.[54] Between 2010 and 2011, Florida instituted a series of major policy changes that were designed to reduce the inappropriate supply of prescription opioids. After these policies were implemented, prescriptions were curtailed and the rate of death from prescription-opioid overdose declined 27% between 2010 and 2012.[13,54] Moreover, these significant declines in prescription-opioid mortality were accompanied by an increase of only 60 deaths related to heroin, with the overall number of total deaths from overdose declining by 535 between 2010 and 2012.[13]

The fourth study, which examined opioid overdoses in New York, showed a 29% reduction in the rate of death from prescription-opioid overdose coupled with declines in the rates of overall and high-dose opioid prescribing in Staten Island, New York, in 2013 after the implementation of targeted and general public health initiatives, including a heavy focus on prescribing behaviors.[15] Importantly, these decreases were not offset by increases in mortality from heroin-involved overdose during the same time period.[15]

Finally, in an investigation of deaths related to heroin and prescription-opioid use in 28 states between 2010 and 2012, Rudd and colleagues found no association between declines in prescription-opioid–related mortality and increases in heroin-related mortality.[55] In fact, they found that increases in the rates of death due to heroin overdose were associated with increases in the rates of death due to prescription-opioid overdose in these states.[55]

Although none of these studies can disprove a potential relationship between policies that are aimed at decreasing the availability of inappropriately prescribed opioids and the motivation for heroin use in some people, the results of these studies consistently suggest that the transition to heroin use was occurring before most of these policies were enacted, and such policies do not appear to have directly led to the overall increases in the rates of heroin use.

CONCLUSIONS

Available data indicate that the nonmedical use of prescription opioids is a strong risk factor for heroin use. Yet, although the majority of current heroin users report having used prescription opioids nonmedically before they initiated heroin use, heroin use among people who use prescription opioids for nonmedical reasons is rare, and the transition to heroin use appears to occur at a low rate.

The transition from nonmedical use of prescription opioids to heroin use appears to be part of the progression of addiction in a subgroup of nonmedical users of prescription opioids, primarily among persons with frequent nonmedical use and those with prescription opioid abuse or dependence. Although some authors suggest that there is an association between policy-driven reductions in the availability of prescription opioids and increases in the rates of heroin use,[16,18] the timing of these shifts, many of which began before policies were robustly implemented, makes a causal link unlikely.

In the majority of studies, the increase in the rates of heroin use preceded changes in prescription-opioid policies, and there is no consistent evidence of an association between the implementation of policies related to prescription opioids and increases in the rates of heroin use or deaths, although the data are relatively sparse. Alternatively, heroin market forces, including increased accessibility, reduced price, and high purity of heroin appear to be major drivers of the recent increases in rates of heroin use.[46,56] Regardless of the causes of the high rates of both nonmedical prescription-opioid use and heroin use, in order to minimize overall opioid-related morbidity and mortality, efforts are needed to help people who are already addicted, in parallel with efforts to prevent people from becoming addicted in the first place.

Addressing the combined and interrelated

opioid epidemics requires comprehensive action, including the prevention of the initiation of nonmedical use of opioids, interventions for persons who have clinically significant complications from opioid use, and improved treatment for those with opioid-use disorders. Prevention efforts should target the major risk factors for the initiation of opioid use, including the excess availability of prescription opioids; these risk factors may be addressed with policy and practice interventions such as the enhanced use of prescription-drug monitoring programs and the development of clinical guidelines to educate clinicians.[14,57] Universal family-based drug-abuse prevention, which has been shown to reduce the rates of initiation of nonmedical use of prescription opioids, may also play an important role.[58] Whether the opioid is heroin or a prescription medication, interventions to reduce morbidity and mortality include expanded access to naloxone in contexts in which overdoses occur[59-61] and increased use of effective treatment for opioid-use disorders, particularly medication-assisted treatment administered for an adequate duration.[62-65]

Fundamentally, prescription opioids and heroin are each elements of a larger epidemic of opioid-related disorders and death. Viewing them from a unified perspective is essential to improving public health. The perniciousness of this epidemic requires a multipronged interventional approach that engages all sectors of society.[14,66]

The views expressed in this article are those of the authors and do not necessarily represent those of the National Institute on Drug Abuse, the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, or the Department of Health and Human Services.

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COMPLAINT

EXHIBIT #10

MMWR Vital Signs

January 1, 2016

Morbidity and Mortality Weekly Report

Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014

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On December 18, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

The United States is experiencing an epidemic of drug overdose (poisoning) deaths. Since 2000, the rate of deaths from drug overdoses has increased 137%, including a 200% increase in the rate of overdose deaths involving opioids (opioid pain relievers and heroin). CDC analyzed recent multiple cause-of-death mortality data to examine current trends and characteristics of drug overdose deaths, including the types of opioids associated with drug overdose deaths. During 2014, a total of 47,055 drug overdose deaths occurred in the United States, representing a 1-year increase of 6.5%, from 13.8 per 100,000 persons in 2013 to 14.7 per 100,000 persons in 2014. The rate of drug overdose deaths increased significantly for both sexes, persons aged 25–44 years and ≥55 years, non-Hispanic whites and non-Hispanic blacks, and in the Northeastern, Midwestern, and Southern regions of the United States. Rates of opioid overdose deaths also increased significantly, from 7.9 per 100,000 in 2013 to 9.0 per 100,000 in 2014, a 14% increase. Historically, CDC has programmatically characterized all opioid pain reliever deaths (natural and semisynthetic opioids, methadone, and other synthetic opioids) as "prescription" opioid overdoses (*1*). Between 2013 and 2014, the age-adjusted rate of death involving methadone remained unchanged; however, the age-adjusted rate of death involving natural and semisynthetic opioid pain relievers, heroin, and synthetic opioids, other than methadone (e.g., fentanyl) increased 9%, 26%, and 80%, respectively. The sharp increase in deaths involving synthetic opioids, other than methadone, in 2014 coincided with law enforcement reports of increased availability of illicitly manufactured fentanyl, a synthetic opioid; however, illicitly manufactured fentanyl cannot be distinguished from prescription fentanyl in death certificate data. These findings indicate that the opioid overdose epidemic is worsening. There is a need for continued action to prevent opioid abuse, dependence, and death, improve treatment capacity for opioid use disorders, and reduce the supply of illicit opioids, particularly heroin and illicit fentanyl.

The National Vital Statistics System multiple cause-of-death mortality files were used to identify drug overdose deaths.* Drug overdose deaths were classified using the *International Classification of Disease, Tenth Revision* (ICD-10), based on the ICD-10 underlying cause-of-death codes X40–44 (unintentional), X60–64 (suicide), X85 (homicide), or Y10–Y14 (undetermined intent) (*2*). Among the deaths with drug overdose as the underlying cause, the type of opioid involved is indicated by the following ICD-10 multiple cause-of-death codes: opioids (T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6); natural and semisynthetic opioids (T40.2); methadone (T40.3); synthetic opioids, other than methadone (T40.4); and heroin (T40.1). Some deaths involve more than one type of opioid; these deaths were included in the rates for each category (e.g., a death involving both a synthetic opioid and heroin would be included in the rates for synthetic opioid deaths and in the rates for heroin deaths). Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S standard population age distribution (*3*). Significance testing was based on the z-test at a significance level of 0.05.

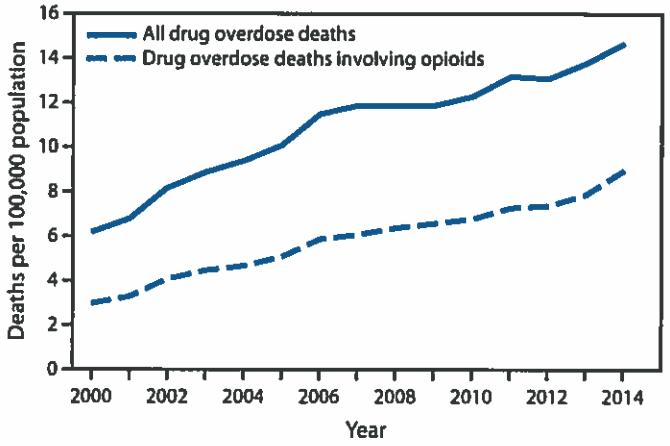
During 2014, 47,055 drug overdose deaths occurred in the United States. Since 2000, the age-adjusted drug overdose death rate has more than doubled, from 6.2 per 100,000 persons in 2000 to 14.7 per 100,000 in 2014 (Figure 1). The overall number and rate of drug overdose deaths increased significantly from 2013 to 2014, with an additional 3,073 deaths occurring in 2014 (Table), resulting in a 6.5% increase in the age-adjusted rate. From 2013 to 2014, statistically significant increases in drug overdose death rates were seen for both males and females, persons aged 25–34 years, 35–44 years, 55–64 years, and ≥65 years; non-Hispanic whites and non-Hispanic blacks; and residents in the Northeast, Midwest and South Census Regions (Table). In 2014, the five states with the highest rates of drug overdose deaths were West Virginia (35.5 deaths per 100,000), New Mexico (27.3), New Hampshire (26.2), Kentucky (24.7) and Ohio (24.6).† States with statistically significant increases in the rate of drug overdose deaths from 2013 to 2014 included Alabama, Georgia, Illinois, Indiana, Maine, Maryland, Massachusetts, Michigan, New Hampshire, New Mexico, North Dakota, Ohio, Pennsylvania, and Virginia.

In 2014, 61% (28,647, data not shown) of drug overdose deaths involved some type of opioid, including heroin. The age-adjusted rate of drug overdose deaths involving opioids increased significantly from 2000 to 2014, increasing 14% from 2013 (7.9 per 100,000) to 2014 (9.0) (Figure 1). From 2013 to 2014, the largest increase in the rate of drug overdose deaths involved synthetic opioids, other than methadone

* Additional information available at http://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm.

† Additional information available at http://www.cdc.gov/drugoverdose/data/statedeaths.html.

FIGURE 1. Age-adjusted rate* of drug overdose deaths† and drug overdose deaths involving opioids§,¶ — United States, 2000–2014



Source: National Vital Statistics System, Mortality file.

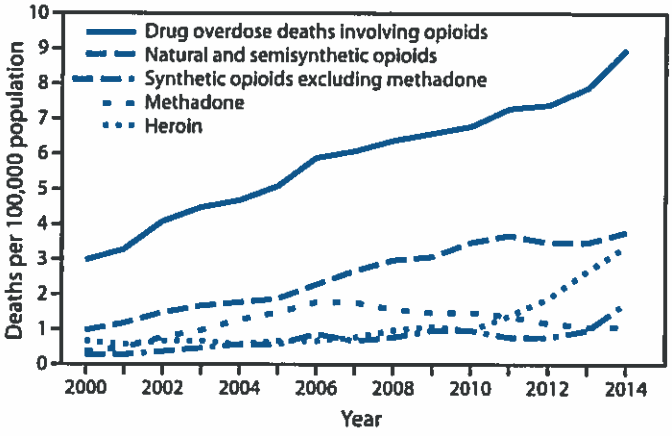
* Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S. standard population age distribution.

† Drug overdose deaths are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

§ Drug overdose deaths involving opioids are drug overdose deaths with a multiple cause-of-death code of T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6. Approximately one fifth of drug overdose deaths lack information on the specific drugs involved. Some of these deaths might involve opioids.

¶ Opioids include drugs such as morphine, oxycodone, hydrocodone, heroin, methadone, fentanyl, and tramadol.

FIGURE 2. Drug overdose deaths* involving opioids,†,§ by type of opioid¶ — United States, 2000–2014



Source: National Vital Statistics System, Mortality file.

* Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S. standard population age distribution.

† Drug overdose deaths involving opioids are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14 with a multiple cause code of T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6.

§ Opioids include drugs such as morphine, oxycodone, hydrocodone, heroin, methadone, fentanyl, and tramadol.

¶ For each type of opioid, the multiple cause-of-death code was T40.1 for heroin, T40.2 for natural and semisynthetic opioids (e.g., oxycodone and hydrocodone), T40.3 for methadone, and T40.4 for synthetic opioids excluding methadone (e.g., fentanyl and tramadol). Deaths might involve more than one drug thus categories are not exclusive.

(e.g., fentanyl and tramadol), which nearly doubled from 1.0 per 100,000 to 1.8 per 100,000 (Figure 2). Heroin overdose death rates increased by 26% from 2013 to 2014 and have more than tripled since 2010, from 1.0 per 100,000 in 2010 to 3.4 per 100,000 in 2014 (Figure 2). In 2014, the rate of drug overdose deaths involving natural and semisynthetic opioids (e.g., morphine, oxycodone, and hydrocodone), 3.8 per 100,000, was the highest among opioid overdose deaths, and increased 9% from 3.5 per 100,000 in 2013. The rate of drug overdose deaths involving methadone, a synthetic opioid classified separately from other synthetic opioids, was similar in 2013 and 2014.

Discussion

More persons died from drug overdoses in the United States in 2014 than during any previous year on record. From 2000 to 2014 nearly half a million persons in the United States have died from drug overdoses. In 2014, there were approximately one and a half times more drug overdose deaths in the United States than deaths from motor vehicle crashes (*4*). Opioids, primarily prescription pain relievers and heroin, are the main drugs associated with overdose deaths. In 2014, opioids were involved in 28,647 deaths, or 61% of all drug overdose deaths; the rate of opioid overdoses has tripled since 2000. The 2014 data demonstrate that the United States' opioid overdose epidemic includes two distinct but interrelated trends: a 15-year increase in overdose deaths involving prescription opioid pain relievers and a recent surge in illicit opioid overdose deaths, driven largely by heroin.

Natural and semisynthetic opioids, which include the most commonly prescribed opioid pain relievers, oxycodone and hydrocodone, continue to be involved in more overdose deaths than any other opioid type. Although this category of opioid drug overdose death had declined in 2012 compared with 2011, and had held steady in 2013, there was a 9% increase in 2014.

Drug overdose deaths involving heroin continued to climb sharply, with heroin overdoses more than tripling in 4 years. This increase mirrors large increases in heroin use across the country (*5*) and has been shown to be closely tied to opioid pain reliever misuse and dependence. Past misuse of prescription opioids is the strongest risk factor for heroin initiation and use, specifically among persons who report past-year dependence or abuse (*5*). The increased availability of heroin, combined with its relatively low price (compared with diverted prescription opioids) and high purity appear to be major drivers of the upward trend in heroin use and overdose (*6*).

The rate of drug overdose deaths involving synthetic opioids nearly doubled between 2013 and 2014. This category includes both prescription synthetic opioids (e.g., fentanyl

TABLE. Number and age-adjusted rates of drug overdose deaths,* by sex, age, race and Hispanic origin,† Census region, and state — United States, 2013 and 2014

Decedent characteristic	2013		2014		% change from 2013 to 2014
	No.	Age-adjusted rate	No.	Age-adjusted rate	
All	43,982	13.8	47,055	14.7	6.5§
Sex					
Male	26,799	17.0	28,812	18.3	7.6§
Female	17,183	10.6	18,243	11.1	4.7§
Age group (yrs)					
0–14	105	0.2	109	0.2	0.0
15–24	3,664	8.3	3,798	8.6	3.6
25–34	8,947	20.9	10,055	23.1	10.5§
35–44	9,320	23.0	10,134	25.0	8.7§
45–54	12,045	27.5	12,263	28.2	2.5
55–64	7,551	19.2	8,122	20.3	5.7§
≥65	2,344	5.2	2,568	5.6	7.7§
Race and Hispanic origin†					
White, non-Hispanic	35,581	17.6	37,945	19.0	8.0§
Black, non-Hispanic	3,928	9.7	4,323	10.5	8.2§
Hispanic	3,345	6.7	3,504	6.7	0.0
Census region of residence					
Northeast	8,403	14.8	9,077	16.1	8.8§
Midwest	9,745	14.6	10,647	16.0	9.6§
South	15,519	13.1	16,777	14.0	6.9§
West	10,315	13.6	10,554	13.7	0.7
State of residence					
Alabama	598	12.7	723	15.2	19.7§
Alaska	105	14.4	124	16.8	16.7
Arizona	1,222	18.7	1,211	18.2	-2.7
Arkansas	319	11.1	356	12.6	13.5
California	4,452	11.1	4,521	11.1	0.0
Colorado	846	15.5	899	16.3	5.2
Connecticut	582	16.0	623	17.6	10.0
Delaware	166	18.7	189	20.9	11.8
District of Columbia	102	15.0	96	14.2	-5.3
Florida	2,474	12.6	2,634	13.2	4.8
Georgia	1,098	10.8	1,206	11.9	10.2§
Hawaii	158	11.0	157	10.9	-0.9
Idaho	207	13.4	212	13.7	2.2
Illinois	1,579	12.1	1,705	13.1	8.3§
Indiana	1,064	16.6	1,172	18.2	9.6§
Iowa	275	9.3	264	8.8	-5.4
Kansas	331	12.0	332	11.7	-2.5
Kentucky	1,019	23.7	1,077	24.7	4.2
Louisiana	809	17.8	777	16.9	-5.1
Maine	174	13.2	216	16.8	27.3§
Maryland	892	14.6	1,070	17.4	19.2§
Massachusetts	1,081	16.0	1,289	19.0	18.8§
Michigan	1,553	15.9	1,762	18.0	13.2§
Minnesota	523	9.6	517	9.6	0.0
Mississippi	316	10.8	336	11.6	7.4
Missouri	1,025	17.5	1,067	18.2	4.0
Montana	137	14.5	125	12.4	-14.5
Nebraska	117	6.5	125	7.2	10.8
Nevada	614	21.1	545	18.4	-12.8
New Hampshire	203	15.1	334	26.2	73.5§
New Jersey	1,294	14.5	1,253	14.0	-3.4
New Mexico	458	22.6	547	27.3	20.8§
New York	2,309	11.3	2,300	11.3	0.0
North Carolina	1,259	12.9	1,358	13.8	7.0
North Dakota	20	2.8	43	6.3	125.0§
Ohio	2,347	20.8	2,744	24.6	18.3§
Oklahoma	790	20.6	777	20.3	-1.5
Oregon	455	11.3	522	12.8	13.3

See table footnotes on the next page.

TABLE. (*Continued*) Number and age-adjusted rates of drug overdose deaths,* by sex, age, race and Hispanic origin,† Census region, and state — United States, 2013 and 2014

Decedent characteristic	2013		2014		% change from 2013 to 2014
	No.	Age-adjusted rate	No.	Age-adjusted rate	
Pennsylvania	2,426	19.4	2,732	21.9	12.9§
Rhode Island	241	22.4	247	23.4	4.5
South Carolina	620	13.0	701	14.4	10.8
South Dakota	55	6.9	63	7.8	13.0
Tennessee	1,187	18.1	1,269	19.5	7.7
Texas	2,446	9.3	2,601	9.7	4.3
Utah	594	22.1	603	22.4	1.4
Vermont	93	15.1	83	13.9	-7.9
Virginia	854	10.2	980	11.7	14.7§
Washington	969	13.4	979	13.3	-0.7
West Virginia	570	32.2	627	35.5	10.2
Wisconsin	856	15.0	853	15.1	0.7
Wyoming	98	17.2	109	19.4	12.8

Source: National Vital Statistics System, Mortality file.

* Deaths are classified using the *International Classification of Diseases, Tenth Revision* (ICD–10). Drug overdose deaths are identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S standard population age distribution.

† Data for Hispanic origin should be interpreted with caution; studies comparing Hispanic origin on death certificates and on census surveys have shown inconsistent reporting on Hispanic ethnicity.

§ Statistically significant change from 2013 to 2014.

and tramadol) and non-pharmaceutical fentanyl manufactured in illegal laboratories (illicit fentanyl). Toxicology tests used by coroners and medical examiners are unable to distinguish between prescription and illicit fentanyl. Based on reports from states and drug seizure data, however, a substantial portion of the increase in synthetic opioid deaths appears to be related to increased availability of illicit fentanyl (*7*), although this cannot be confirmed with mortality data. For example, five jurisdictions (Florida, Maryland, Maine, Ohio, and Philadelphia, Pennsylvania) that reported sharp increases in illicit fentanyl seizures, and screened persons who died from a suspected drug overdose for fentanyl, detected similarly sharp increases in fentanyl-related deaths (*7*).§ Finally, illicit fentanyl is often combined with heroin or sold as heroin. Illicit fentanyl might be contributing to recent increases in drug overdose deaths involving heroin. Therefore, increases in illicit fentanyl-associated deaths might represent an emerging and troubling feature of the rise in illicit opioid overdoses that has been driven by heroin.

The findings in this report are subject to at least three limitations. First, several factors related to death investigation might affect estimates of death rates involving specific drugs. At autopsy, toxicological laboratory tests might be performed to determine the type of drugs present; however, the substances tested for and circumstances under which the tests are performed vary by jurisdiction. Second, in 2013 and 2014, 22% and 19% of drug overdose deaths, respectively, did not include information on the death certificate about the specific types of drugs involved. The percent of overdose deaths with specific drugs identified on the death certificate varies widely by state. Some of these deaths might have involved opioids. This increase in the reporting of specific drugs in 2014 might have contributed to some of the observed increases in drug overdose death rates involving different types of opioids from 2013 to 2014. Finally, some heroin deaths might be misclassified as morphine because morphine and heroin are metabolized similarly (*8*), which might result in an underreporting of heroin overdose deaths.

To reverse the epidemic of opioid drug overdose deaths and prevent opioid-related morbidity, efforts to improve safer prescribing of prescription opioids must be intensified. Opioid pain reliever prescribing has quadrupled since 1999 and has increased in parallel with overdoses involving the most commonly used opioid pain relievers (*1*). CDC has developed a draft guideline for the prescribing of opioids for chronic pain to address this need.¶

In addition, efforts are needed to protect persons already dependent on opioids from overdose and other harms. This includes expanding access to and use of naloxone (a safe and effective antidote for all opioid-related overdoses)** and increasing access to medication-assisted treatment, in combination with behavioral therapies (*9*). Efforts to ensure access to integrated prevention services, including access to syringe service programs when available, is also an important

§ Additional information available at http://pub.lucidpress.com/NDEWSFentanyl/.

¶ Additional information available at http://www.cdc.gov/drugoverdose/prescribing/guideline.html.

** Additional information available at https://store.samhsa.gov/shin/content/SMA13-4742/Overdose_Toolkit_2014_Jan.pdf.

Summary

What is already known on this topic?

The rate for drug overdose deaths has increased approximately 140% since 2000, driven largely by opioid overdose deaths. After increasing since the 1990s, deaths involving the most commonly prescribed opioid pain relievers (i.e., natural and semisynthetic opioids) declined slightly in 2012 and remained steady in 2013, showing some signs of progress. Heroin overdose deaths have been sharply increasing since 2010.

What is added by this report?

Drug overdose deaths increased significantly from 2013 to 2014. Increases in opioid overdose deaths were the main factor in the increase in drug overdose deaths. The death rate from the most commonly prescribed opioid pain relievers (natural and semisynthetic opioids) increased 9%, the death rate from heroin increased 26%, and the death rate from synthetic opioids, a category that includes illicitly manufactured fentanyl and synthetic opioid pain relievers other than methadone, increased 80%. Nearly every aspect of the opioid overdose death epidemic worsened in 2014.

What are the implications for public health practice?

Efforts to encourage safer prescribing of opioid pain relievers should be strengthened. Other key prevention strategies include expanding availability and access to naloxone (an antidote for all opioid-related overdoses), increasing access to medication-assisted treatment in combination with behavioral therapies, and increasing access to syringe service programs to prevent the spread of hepatitis C virus infection and human immunodeficiency virus infections. Public health agencies, medical examiners and coroners, and law enforcement agencies can work collaboratively to improve detection of and response to outbreaks associated with drug overdoses related to illicit opioids.

consideration to prevent the spread of hepatitis C virus and human immunodeficiency virus infections from injection drug use.

Public health agencies, medical examiners and coroners, and law enforcement agencies can work collaboratively to improve detection of outbreaks of drug overdose deaths involving illicit opioids (including heroin and illicit fentanyl) through improved investigation and testing as well as reporting and monitoring of specific drugs, and facilitate a rapid and effective response that can address this emerging threat to public health and safety (*7*). Efforts are needed to distinguish the drugs contributing to overdoses to better understand this trend.

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COMPLAINT

EXHIBIT #11

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REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies

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CHRONIC PAIN NOT CAUSED BY CANCER IS AMONG THE MOST PREVALENT and debilitating medical conditions but also among the most controversial and complex to manage. The urgency of patients' needs, the demonstrated effectiveness of opioid analgesics for the management of acute pain, and the limited therapeutic alternatives for chronic pain have combined to produce an overreliance on opioid medications in the United States, with associated alarming increases in diversion, overdose, and addiction. Given the lack of clinical consensus and research-supported guidance, physicians understandably have questions about whether, when, and how to prescribe opioid analgesics for chronic pain without increasing public health risks. Here, we draw on recent research to address common misconceptions regarding the abuse-related risks of opioid analgesics and highlight strategies to minimize those risks.

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SOURCE OF THE OPIOID EPIDEMIC

More than 30% of Americans have some form of acute or chronic pain.[1,2] Among older adults, the prevalence of chronic pain is more than 40%.[2] Given the prevalence of chronic pain and its often disabling effects, it is not surprising that opioid analgesics are now the most commonly prescribed class of medications in the United States.[3] In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers.[4,5] Of these prescriptions, 65% were for short-term therapy (<3 weeks),[6] but 3 to 4% of the adult population (9.6 million to 11.5 million persons) were prescribed longer-term opioid therapy.[7] Although opioid analgesics rapidly relieve many types of acute pain and improve function, the benefits of opioids when prescribed for chronic pain are much more questionable.[8]

However, two major facts can no longer be questioned. First, opioid analgesics are widely diverted and improperly used, and the widespread use of the drugs has resulted in a national epidemic of opioid overdose deaths and addictions. More than a third (37%) of the 44,000 drug-overdose deaths that were reported in 2013 (the most recent year for which estimates are available) were attributable to pharmaceutical opioids; heroin accounted for an additional 19%. At the same time, there has been a parallel increase in the rate of opioid addiction, affecting approximately 2.5 million adults in 2014.[9] Second, the major source of diverted opioids is physician prescriptions.[10,11] For these reasons, physicians and medical associations have begun questioning prescribing practices for opioids, particularly as they relate to the management of chronic pain. Moreover, many physicians admit that they are not confident about how to prescribe opioids safely,[12] how to detect abuse or emerging addiction, or even how to discuss these issues with their patients.[13]

This review is not intended as clinical instruction in chronic pain management;

Table 1. Misconceptions Regarding Opioids and Addiction.*

Addiction is the same as physical dependence and tolerance. This misconception leads some clinicians to avoid prescribing opioids to patients who would benefit from them and many patients to be afraid of taking opioids as prescribed.

Addiction is simply a set of bad choices. This misconception contributes to the discrimination against patients with addiction and to the willful ignorance by many in the health care system about modern treatment methods. It also promotes mistrust of patients by clinicians and prevents affected patients from seeking help for their addiction.

Pain protects patients from addiction to their opioid medications. This misconception can lead to overconfidence and overprescribing among clinicians as well as failure to monitor and recognize addictive behaviors or to intervene properly when they emerge. Research has shown that patients who are prescribed opioid medications for pain can become addicted to them even when the drugs are taken as prescribed.

Only long-term use of certain opioids produces addiction. The misconception that addiction is simply the property of certain opioid drugs promotes overprescribing of certain types of opioids that may be as risky as types that are well known to be associated with addiction. An improved prescribing practice in the management of acute pain is a necessary step in the control of opioid diversion and overdose, since the overprescription of opioids for acute pain is the main source of drug diversion.

Only patients with certain characteristics are vulnerable to addiction. Certain conditions do increase the vulnerability to addiction. These include substance-use disorder (including abuse of alcohol, nicotine, and illicit drugs), developmental stage (adolescents are more vulnerable than adults), and certain mental illnesses (e.g., attention deficit–hyperactivity disorder and major depressive disorder). Although some patients are more vulnerable than others, no patient is immune to addiction.

Medication-assisted therapies are just substitutes for heroin or opioids. The use of opioid-agonist medications such as methadone and buprenorphine for opioid addiction has led to the misconception that such drugs are just substitutes for the opioid being abused. Although these medications are opioid agonists, their slower brain pharmacokinetics along with their more stable concentrations help to stabilize physiologic processes that are disrupted by intermittent abuse of opioids. The use of these drugs also protects against risks associated with opioid abuse while facilitating recovery.[18-20]

* These misconceptions were drawn directly from questions submitted by physicians to two major websites for pain-management specialists (the American Academy of Pain Management and the American Pain Society).

for that, we suggest recent clinical guidelines.[14-17] Instead, this review focuses on the pharmacologic properties of opioids that underlie both their therapeutic effects and their abuse-producing effects and on the ways in which these properties should inform us in correcting common clinical misconceptions that interfere with the proper prescription and monitoring of opioids in the management of chronic pain (Table 1).

WHY OPIOID MEDICATIONS ARE DIVERTED AND ABUSED

Opioid medications exert their analgesic effects predominantly by binding to mu-opioid receptors. Mu-opioid receptors are densely concentrated in brain regions that regulate pain perception (periaqueductal gray, thalamus, cingulate cortex, and insula), including pain-induced emotional responses (amygdala), and in brain reward regions (ventral tegmental area and nucleus accumbens) that underlie the perception of pleasure and well-being. This explains why opioid medications can produce both analgesia and euphoria. Mu-opioid receptors in other brain regions and in peripheral organs account for other common opioid effects. In particular, mu-opioid receptors in the brain stem are mainly responsible for the respiratory depression associated with opioid-overdose incidents and deaths[21,22] (Fig. 1).

Opioids not only directly activate these brain analgesia and reward regions but also concurrently mediate a learned association between receipt of the drug and the physiological and perceptual effects of the drug — a type of Pavlovian conditioning.[23] Repeated receipt of opioids strengthens these learned associations and over time becomes part of the desire (craving) for the drug's effects — analgesic or pleasurable.[24] For a patient in chronic pain, even mild levels of pain can trigger the learned associations between pain and drug relief, which are manifested as an urge for relief. Such a conditioned urge for relief from even mild pain can lead to the early, inappropriate use of an opioid outside prescribed scheduling.

Opioid medications vary with respect to their affinity and selectivity for the mu-opioid receptor, since some also bind to kappa- or delta-opioid receptors or to other neurotransmitter receptors and transporters. There is also considerable variation among the drugs with respect to their pharmacokinetics and bioavailability. When combined, these pharmacologic properties affect the rapidity of onset, potency, and duration of both the analgesic and pleasurable effects of opioids.

The effects of opioids — particularly their rewarding effects — are accentuated most when the drugs are delivered rapidly into the brain.[25] This is why diverted opioids that are taken for their rewarding effects are frequently injected. This also explains why the Food and Drug Administration has encouraged and approved abuse-deterrent formulations that are designed to prevent the injection of pharmaceutical opioids[26] (Table 2).

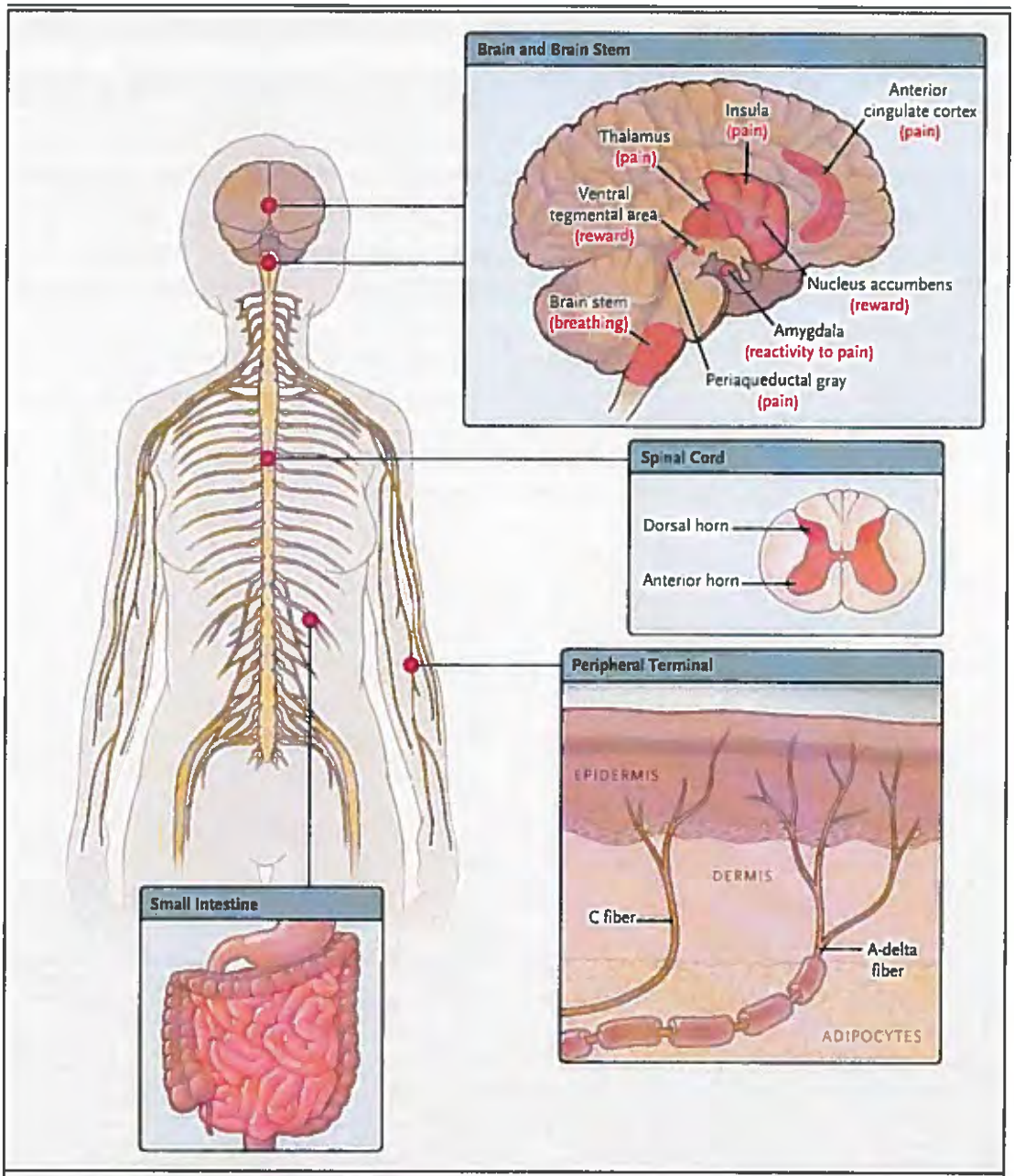

Figure 1. Location of Mu-Opioid Receptors.

Shown are the locations of mu-opioid receptors in the human brain, with high concentration in the thalamus, periaqueductal gray, insula, and anterior cingulate (regions involved with pain perception), in the ventral tegmental area and nucleus accumbens (regions involved with reward), in the amygdala (a region involved with emotional reactivity to pain), and in the brain stem (nuclei that regulate breathing). In the spinal cord, a high concentration of mu-opioid receptors is located in the dorsal horn. Mu-opioid receptors in peripheral terminals modulate the perception of pain, and receptors in the small intestine regulate gut motility.

OPIOID-INDUCED TOLERANCE AND PHYSICAL DEPENDENCE

There is lingering misunderstanding among some physicians about the important differences between physical dependence and addiction. The repeated administration of any opioid almost inevitably results in the development of tolerance and physical dependence. These predictable phenomena reflect counter-adaptations in opioid

Table 2. Formulations for Deterrence of Abuse.

When opioids are diverted because of their rewarding effects, they are typically taken at higher doses than were originally prescribed. In other cases, the pills are crushed so that the drug can be snorted, smoked, or injected. These routes of administration result in faster drug delivery into the brain, which in turn is associated with a rapid and more intense drug effect. Thus, strategies for abuse-deterrent formulations have been developed to minimize the likelihood that the opioids will be injected or snorted or taken at higher doses than prescribed.[27,28] These strategies include the following:

Combining the opioid agonist with an antagonist. Mixing the opioid with naloxone or naltrexone will interfere with the opioid effects if the drug is injected but not if it is taken orally or sublingually. Examples include Embeda (morphine sulfate plus naltrexone hydrochloride) and Targiniq ER (oxycodone plus naloxone).

Delivering the opioid in a form that cannot be crushed and extracted. Examples of such drug-delivery technologies include opioids approved by Food and Drug Administration (FDA) in abuse-deterrent formulations such as Hysingla (hydrocodone) and the new formulation of OxyContin (oxycodone), as well as opioids not approved as abuse-deterrent formulations, including Exalgo (hydromorphone), Nucynta ER (tapentadol), Opana ER (oxymorphone), Oxecta (oxycodone), and Xartemis (oxycodone and acetaminophen).

Combining the opioid with a substance that triggers an adverse response. If the drug is tampered with or used at a higher dose than indicated, such formulations are designed to produce adverse results. Examples include Lomotil (diphenoxylate hydrochloride plus atropine) and Acurox (oxycodone plus niacin).

Developing prodrugs that require enzymatic activation. Such formulations could provide a chemical barrier to in vitro conversion into the active opioid. There are currently no abuse-deterrent formulations approved by the FDA that use this strategy. Examples being developed include prodrugs for hydrocodone, oxycodone, and hydromorphone that require molecular cleavage by trypsin in the digestive system to release the parent opioid.

receptors and their intracellular signaling cascades.[29] These short-term results of repeated opioid administration resolve rapidly after discontinuation of the opioid (i.e., in a few days to a few weeks, depending on the duration of exposure, type of opioid, and dose). In contrast, addiction will occur in only a small percentage of patients exposed to opioids. Addiction develops slowly, usually only after months of exposure, but once addiction develops, it is a separate, often chronic medical illness that will typically not remit simply with opioid discontinuation and will carry a high risk of relapse for years without proper treatment. The molecular processes responsible for addiction are also distinct from those underlying tolerance and physical dependence, and so are the clinical consequences.

Tolerance leads to a decrease in opioid potency with repeated administration. Thus, prescribing opioids long-term for their analgesic effects will typically require increasingly higher doses in order to maintain the initial level of analgesia — up to 10 times the original dose.[30] Similarly, tolerance with respect to the rewarding effects of opioids leads to the characteristic dose escalation seen in opioid addiction, which can result in daily doses of up to 800 morphine milligram equivalents (MME, the conversion factor used to facilitate comparison of potency among opioids).[31]

Some opioid effects show tolerance after a single dose,[32] whereas for others, tolerance occurs more slowly.[29] In particular, tolerance to the analgesic and euphoric effects of opioids develops quickly, whereas tolerance to respiratory depression develops more slowly,[33,34] which explains why increases in dose by the prescriber or patient to maintain analgesia (or reward) can markedly increase the risk of overdose.

Physical dependence underlies the physiological adaptations that are responsible for the emergence of withdrawal symptoms on the abrupt discontinuation of opioids. Withdrawal symptoms (e.g., piloerection, chills, insomnia, diarrhea, nausea, vomiting, and muscle aches) vary appreciably in severity (from not noticeable to quite uncomfortable) and duration (1 to 14 days) on the basis of the type, dose, and duration of opioid prescribed.[35,36]

In the context of chronic pain management, the discontinuation of opioids requires dose tapering in order to prevent the emergence of such withdrawal symptoms. In some patients, the repeated use of opioids can also lead to hyperalgesia, which is a state of heightened pain sensitivity.[37,38] In the clinical context, hyperalgesia can lead to inappropriate increases in opioid doses, which further exacerbate rather than ameliorate pain.[39] In the case of hyperalgesia, dose tapering or tapering to discontinuation is a better pain-relief strategy.[40]

Unlike tolerance and physical dependence, addiction is not a predictable result of opioid prescribing. Addiction occurs in only a small percentage of persons who are exposed to opioids — even among those with preexisting vulnerabilities (Table 3). Older medical texts and several versions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) either overemphasized the role of tolerance and physical dependence in the definition of addiction or equated these processes (DSM-III and DSM-IV). However, more recent studies have shown that the molecular mechanisms underlying addiction are distinct

from those responsible for tolerance and physical dependence, in that they evolve much more slowly, last much longer, and disrupt multiple brain processes.[57]

Cardinal features of addiction include a pronounced craving for the drug, obsessive thinking about the drug, erosion of inhibitory control over efforts to refrain from drug use, and compulsive drug taking (DSM-5). These behavioral changes in turn are associated with structural and functional changes in the reward, inhibitory, and emotional circuits of the brain.[58,59] Clinical studies have also shown that the ability of opioids to produce addiction is genetically modulated, with heritability rates similar to those of diabetes, asthma, and hypertension.[60,61] For these reasons, we do not know the total dose or the duration of opioid administration that will reliably produce addiction. However, we do know that the risk of opioid addiction varies substantially among persons, that genetic vulnerability accounts for at least 35 to 40% of the risk associated with addiction,[62-64] and that adolescents are at increased risk because of the enhanced neuroplasticity of their brains and their underdeveloped frontal cortex, which is necessary for self-control.[52,62] Hence, in adolescents, the risks and benefits of prescribing opioids for pain management need to be even more carefully weighed than in adults.

In a person with an opioid addiction, discontinuation of the opioid will rapidly reverse the tolerance and physical dependence within days or a couple of weeks. In contrast, the underlying changes that are associated with addiction will persist for months and even years after the discontinuation of opioids.[65] This finding is clinically relevant, because after abstinence from opioids, addicted patients are particularly vulnerable to overdosing: their intense drive to take the drug persists, but the tolerance that previously protected them from overdosing is no longer present. These effects explain the high risk of overdosing among persons with an opioid addiction after they have been released from prison or from a detoxification program.[66,67]

Table 3. Factors Associated with the Risk of Opioid Overdose or Addiction.

Factor	Risk
Medication-related	
Daily dose >100 MME*	Overdose,[8] addiction[8]
Long-acting or extended-release formulation (e.g., methadone, fentanyl patch)	Overdose[14,41]
Combination of opioids with benzodiazepines	Overdose[42]
Long-term opioid use (>3 mo)†	Overdose,[43] addiction[44]
Period shortly after initiation of long-acting or extended-release formulation (<2 wk)	Overdose[45]
Patient-related	
Age >65 yr	Overdose[46]
Sleep-disordered breathing‡	Overdose[47]
Renal or hepatic impairment§	Overdose[48]
Depression	Overdose, addiction[49]
Substance-use disorder (including alcohol)	Overdose,[50] addiction[49]
History of overdose	Overdose[51]
Adolescence	Addiction[52]

* The risk of opioid overdose increases in a dose–response manner at opioid doses of more than 20 morphine milligram equivalents (MME).
† Although addiction is associated with long-term but not short-term opioid use, the prescription of a higher quantity of opioids than is needed for acute pain contributes substantially to the availability of opioids for diversion and abuse.
‡ Sleep-disordered breathing refers to conditions that manifest as abnormal breathing patterns during sleep and includes obstructive sleep apnea and central sleep apnea.[53]
§ Patients with these disorders are at increased risk because the disposition of various opioid drugs is affected by hepatic and renal impairments, which reduce drug clearance and increase bioavailability.[54-56]

MITIGATION STRATEGIES

The rewarding effects of opioids play a major role in the risks of opioid diversion, overdose, and addiction. However, the likelihood and severity of these risks are largely independent and governed by different factors. All these risks are present to some degree with all opioids and with all pain diagnoses. This means that no single or simple change in prescribing behavior can be expected to alleviate all risks while properly managing pain. For example, these risks cannot be mitigated simply by restricting prescribing to a particular type of opioid or by avoiding the prescription of opioids to a particular type of patient. However, there are common strategies that can help mitigate all risks, including limiting the prescribed opioid to the lowest effective dose for the shortest effective duration (for both acute and chronic pain) without compromising effective analgesia. Regular monitoring and reassessment provide opportunities to minimize the risks associated with long-term opioid use by allowing for the tapering and discontinuing of opioids among patients who are not receiving a

Table 4. Mitigation Strategies against Opioid Diversion and Misuse.

Several mitigation strategies for risk assessment of opioid misuse have been proposed.[74] These include the following:

Screening tools to identify patients with a substance-use disorder. Such tools include the Opioid Risk Tool; the Screener and Opioid Assessment for Patients with Pain (SOAPP), version 1.0; SOAPP-Revised; and the Brief Risk Interview; or the use of a simple question such as "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" since patients who score above a certain threshold (e.g., ≥1 to the sample question) may be at increased risk for opioid abuse.[75]

Use of data from the Prescription Drug Monitoring Program. Such data can be used to identify doctor shopping, which is frequently an indication of drug misuse or diversion.

Use of urine drug screening. Such screening, which can be performed before prescription of opioids and periodically as part of regular follow-up, can provide information on drug use not reported by patients and may help in identifying patients who are not taking their prescribed opioids and might be diverting them.

Doctor–patient agreement on adherence. Such personal contracts can help doctors in monitoring a patient's adherence to prescribed opioid medications.

However, a recent review of the evidence showed that only limited data are available regarding the efficacy of any of these strategies.[76]

clear benefit or among those who are engaging in practices that increase the risk of overdose (e.g., consumption of high doses of alcohol, concurrent use of benzodiazepines, and poor adherence to opiate medications).[68]

PREVENTING DRUG DIVERSION

The most common form of diversion is the transfer of opioid analgesics by patients who have received legitimately prescribed opioids to family members or friends who are usually trying to self-medicate a generic pain.[69] This type of diversion applies to prescriptions given for the management of either chronic or acute pain and would be best managed by educating patients on the dangers of sharing their medications and on the importance of safe storage and disposal.[70]

Approximately 7 to 10% of diversion occurs among patients who feign pain to acquire prescribed opioids,[71] usually with the goal of maintaining their addiction, and who will often attempt to acquire opioids from multiple physicians (doctor shopping).[71-73] Physicians have attempted to identify dissembling or addicted patients through screening instruments or through detection of so-called aberrant behaviors that are thought to be indicative of addiction (Table 4).[77] However, the most recent review of patient screening efforts showed no evidence that any scale or procedure was effective.[8] Risks of diversion through doctor shopping are best mitigated by the full participation of all prescribers in Prescription Drug Monitoring Programs (PDMPs). PDMPs are statewide electronic databases that collect information on prescription and dispensing of controlled prescription drugs (including opioid drugs) and were designed to monitor information pertaining to suspected abuse or diversion.[78] Although these data have been shown to help health care professionals reduce doctor shopping and overdoses,[79-81] their use by health care providers is inconsistent.[82-84] This in part reflects the fact that PDMPs are voluntary programs in many states. Although 25 states and the District of Columbia update their databases daily, as of this writing, only Oklahoma provides real-time reporting.[85] In addition, only 22 of 49 PDMPs share information across states.[86] Another obstacle is that access to PDMP data requires a computer that is separate from that used to access electronic health records. However, implementation and consistent use will be facilitated by rapid changes in laws to require mandatory consultation of a PDMP before prescribing, advances in electronic technologies to deliver PDMP information in real time, better integration of PDMPs with electronic health records, and access of PDMP data across state lines.[87]

REDUCING RISK OF OVERDOSE

The rate of death from opioid overdose has quadrupled during the past 15 years in the United States.[88] Researchers at the Centers for Disease Control and Prevention have estimated that 28,647 drug overdose deaths (61%) in 2014 in the United States involved some type of opioid, including heroin.[89] Even more prevalent are nonfatal opioid overdoses that require medical care in a hospital or emergency department. Such events have increased by a factor of six in the past 15 years.[90]

The contributing factors associated with overdose can be divided into those associated with the opioid itself (type, dose, potency, and duration of action) and those associated with critical features of the patient (Table 3). Although the use of any opioid can lead to overdose, research suggests that exposure to higher doses of all opioids increases the risk of overdose. Opioid doses of more than 100 MME[91,92] are disproportionately associated with overdose-related hospital

admissions and deaths[45] (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The use of long-acting opioids, such as methadone and oxycodone, has also been associated with an increased risk of overdose.[45]

Several identifiable characteristics among patients have been reliably associated with an elevated risk of opioid overdose (Table 3). Included among these factors are a history of overdose,[51,93] a history of addiction to any substance (but particularly alcohol, benzodiazepines, or opioids),[93] and health problems associated with respiratory depression or concurrent prescription of any medication that has a depressive effect on the respiratory system, such as benzodiazepines and sedative hypnotics.[88] The presence of renal or hepatic dysfunction also increases the risk of overdose, since in patients with either of these conditions, the clearance of many opioid drugs is impaired, which leads to higher and longer-lasting drug levels in blood.[54,55] Finally, because some cases of overdose may be purposeful suicide attempts,[94,95] a history of suicidal thoughts or attempts and a diagnosis of major depression are also markers for an elevated risk of overdose.

Recommended mitigation strategies include an overdose risk assessment (Table 3) and urine drug screening before prescription or represcription of opioids (to verify absence of drugs of abuse). The identification of these risks does not automatically rule out opioids as part of effective pain management. However, these risks do indicate the needs for much greater education of the patient (and the patient's family) about overdose risks, the use of an opioid treatment agreement,[96] increased caution in prescribing high opioid doses or long-acting opioids, more frequent clinical follow-up, and, potentially, a prescription for and instruction in the use of naloxone, an opioid antagonist that can reverse an opioid-induced overdose. Indeed, expanding access to naloxone has been shown to significantly reduce the rate of death from opioid overdoses.[97]

MINIMIZING THE RISK OF ADDICTION

For many years, it was believed that pain protected against the development of addiction to opioid medications. However, epidemiologic studies of opioid addiction among patients in pain, as well as preclinical studies of addiction in animal models of chronic pain,[24,98,99] have disproved this belief. Although published estimates of iatrogenic addiction vary substantially from less than 1% to more than 26% of cases,[100] part of this variability is due to confusion in definition. Rates of carefully diagnosed addiction have averaged less than 8% in published studies, whereas rates of misuse, abuse, and addiction-related aberrant behaviors have ranged from 15 to 26%.[101-103] A small (estimated at 4%) but growing percentage of persons who are addicted to prescription opioids transition to heroin,[1] mainly because heroin is typically cheaper and in some instances easier to obtain than opioids.

Clinical efforts to prevent the emergence of addiction can be initiated in primary care settings. Assessment of addiction risks before opiates are prescribed is recommended as a mitigation strategy (Table 3). Emerging signs of addiction can be identified and managed through regular monitoring, including urine drug testing before every prescription is written, to assess for the presence of other opioids or drugs of abuse. Responsible physicians should be prepared to make a referral for specialty addiction treatment when indicated. Although addiction is a serious chronic condition, recovery is a predictable result of comprehensive, continuing care and monitoring.[104] In particular, the use of medication-assisted therapy in managing opioid addiction among patients with co-occurring pain significantly improves outcomes.[105]

On the basis of research and clinical evidence, the Department of Health and Human Services recently launched an initiative to reduce opioid overdoses and addiction that focuses on improving opioid prescribing practices to reduce opioid-use disorders and overdoses, expanding the use of naloxone to prevent overdoses, and extending the use of medication-assisted treatment to reduce opioid-use disorders and overdoses.[106]

CONCLUSIONS

It is no longer possible to simply continue previous practices with respect to the management of chronic pain. The associated risks of opioid diversion, overdose, and addiction demand change. Although there are no simple solutions, we recommend three practice and policy changes that can reduce abuse-related risks and improve the treatment of chronic pain.

Table 5. Alternative Treatments for Chronic Pain.*

Nonpharmacologic
Cognitive-behavioral therapy[109]
Exercise therapy[110-113]
Complementary medicine[114] (e.g., yoga, meditation, acupuncture)
Nonopioid analgesics
Acetaminophen
Nonselective nonsteroidal antiinflammatory drugs; recommended as first-line pharmacotherapy for osteoarthritis[115] and low back pain[116] in multiple guidelines
Cyclooxygenase-2 inhibitors
Anticonvulsants (gabapentin or pregabalin)†
Antidepressants (tricyclics and serotonin and norepinephrine reuptake inhibitors)†
Interventional and neural-stimulation therapies
Epidural injection; may provide short-term improvement for certain pain-associated conditions (e.g., lumbar radiculopathy)[1]
Brain, spinal cord, and nerve stimulation, including transcranial magnetic stimulation, transcranial direct current stimulation, electrical deep-brain stimulation, and stimulation devices for peripheral nerves or tissues[117-120]
Biofeedback
Electromyography to help patients learn to control muscle tension and electroencephalography to help patients learn to influence brain electrical signals in order to modulate pain; may be beneficial in treatment of headaches, some forms of chronic back pain, and other pain disorders[121]
Neurofeedback with the use of functional magnetic resonance imaging as a supplemental approach for chronic pain management[122]

* Evidence of efficacy varies for these strategies, and research is ongoing to assess their value in the management of chronic pain.
† Multiple guidelines recommend the use of antidepressant and anticonvulsant medications as either first-line or second-line treatment for neuropathic pain.[123]

INCREASED USE OF SCIENCE-SUPPORTED PRESCRIBING AND MANAGEMENT PRACTICES

The extended prescription of opioids (>8 weeks) for the treatment of chronic pain has questionable benefits for individual patients and presents substantial public health risks.[8] The risks of overdose and addiction from this prescribing practice — both among patients with chronic pain and the public at large — increase with higher doses (>100 MME), longer duration of prescribing, and perhaps the use of long-acting opioids. Despite these facts, a Medicaid study showed that more than 50% of opioid prescriptions were for doses higher than 90 MME and for periods of more than 6 months.[107] Better results can be obtained by using the most contemporary guidelines for pain management.[14]

INCREASED MEDICAL SCHOOL TRAINING ON PAIN AND ADDICTION

Very few medical schools offer adequate training in pain management, and still fewer offer even one course in addiction. The result is that even experienced clinicians are unsure about how to deal with fundamental and omnipresent clinical issues in their practices. Many motivated, well-intentioned physicians do not know whether to prescribe opioids for pain management and, if so, which ones and for how long. Still fewer understand the pharmacologic or clinical relationships among tolerance, physical dependence, and addiction.[108] This education is particularly critical for primary care practitioners, who prescribe more than 70% of opioid analgesics.

INCREASED RESEARCH ON PAIN

At a recent workshop at the National Institutes of Health on the role of opioids in the treatment of chronic pain, attendants recommended several areas of research that are needed for improved clinical practice guidelines. These areas included how to differentiate the unique properties of acute and chronic pain and how to describe the process by which acute pain transitions into chronic pain.[8] Discovery-oriented research was also recommended to identify new, potent nonopioid analgesics and other pain-treatment strategies (Table 5). Access to biomarkers of pain and analgesia that take advantage of neuroimaging technologies or genetic analyses would accelerate the development of new medications and allow for more personalized clinical interventions for pain management.

Dr. McLellan reports receiving fees for serving on the board of directors of Indivior Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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COMPLAINT

EXHIBIT #12

Califf NEJM

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SPECIAL REPORT

A Proactive Response to Prescription Opioid Abuse

Robert M. Califf, M.D., Janet Woodcock, M.D., and Stephen Ostroff, M.D.

We at the Food and Drug Administration (FDA) continue to be deeply concerned about the growing epidemic of opioid abuse, addiction, and overdose — an epidemic directly related to the increasingly widespread misuse of powerful opioid pain medications. As the federal agency charged with ensuring that the drugs used by the U.S. public are both effective and safe, we are committed to working in partnership with other government agencies, health care providers, the medical products industry and, most important, patients and their families to deal proactively with this unfolding public health crisis, which has already profoundly affected individuals, families, and communities throughout our country. We will do so while also safeguarding appropriate access to vitally important pain medications for the patients who need them (Table 1).

BACKGROUND

Over the course of a given year, approximately 100 million people in the United States suffer from pain. Some 9 million to 12 million of them have chronic or persistent pain, while the remainder have short-term pain from injuries, illnesses, or medical procedures. All of them should benefit from skillful and appropriate pain management, which may include the judicious use of opioid medicines in conjunction with other methods of treatment or in circumstances in which nonaddictive therapies are insufficient to control pain.

As physicians, we have treated both the intense suffering caused by acute pain and chronic pain with all its exhausting and debilitating consequences. But we have also witnessed the devastating results of opioid misuse and abuse, such as the addiction of patients who have been prescribed opioids for pain treatment and, increasingly, diversion to people for whom the prescription was not written. Many Americans are now addicted to prescription opioids, and the number of deaths due to prescription opioid overdose is unacceptable. This past month, our sister agency, the Centers for Disease Control and Prevention (CDC), estimated that in 2014 there were almost 19,000 overdose deaths in the United States associated with prescription opioids (Rudd R, CDC: personal communication).

Because protecting the public by ensuring the safety, efficacy, and quality of drugs is an essential part of the FDA's mission, it is appropriate to examine the agency's actions in coping with the public health crisis of opioid misuse. As FDA leaders and as physicians, we believe that these efforts must be founded on two complementary principles: that the United States must deal aggressively with opioid misuse and addiction, and at the same time, that it must protect the well-being of people experiencing the devastating effects of acute or chronic pain. It is a difficult balancing act, but we believe that the continuing escalation of the negative consequences of opioid use compels us to comprehensively review our portfolio of activities, reassess our strategy, and take aggressive actions when there is good reason to believe that doing so will make a positive difference.

We are launching this renewed effort in the context of a broad national campaign that includes a major initiative led by the Department of Health and Human Services (HHS)[1] designed to attack the problem from every angle. The number of annual opioid prescriptions written in the United States is now roughly equal to the number of adults in the population[2]; given these numbers, simply reinforcing opioid-related activities that are within the FDA's traditional regulatory scope will not suffice to stem the tide. Instead, we must work more closely with key federal agencies (including many within

Table 1. Responding to Prescription Opioid Abuse.

Issue	FDA Response
Balancing individual need and societal risk. Patients require access to safe and effective pain medication, but both individuals and society must be protected from the effects of opioid misuse.	The FDA will consult with partners including the National Academy of Medicine to craft a framework for opioid review, approval, and monitoring that balances individual needs for pain control with the risk of addiction, as well as the broader public health consequences of opioid abuse and misuse.
Meeting the need for timely action. The evolving threat of opioid abuse requires a flexible interim approach while the full policy framework is in development.	The FDA Science Board will convene in March to advise on the role of pharmaceuticals in pain management, development of alternative pain medications, and postmarketing surveillance activities. Multiple other actions will also occur over the next several months, including an evaluation of the existing Risk Evaluation and Mitigation Strategy (REMS) requirements for extended-release/long-acting (ER/LA) opioids. An advisory committee will consider this review and offer advice regarding possible expansion of the scope and content of prescriber education and whether to expand the REMS program to include immediate-release opioids, potentially increasing the number of prescribers receiving training on pain management and safe prescribing.
Reviewing labeling and postmarketing surveillance requirements. Current labeling requirements include detailed instructions, and manufacturers are required to conduct postmarketing safety surveillance and research studies, but these measures may need to be reevaluated.	The FDA will revise postmarketing requirements, expanding the requirements for drug companies to generate postmarketing data on long-term impact of ER/LA opioid use to provide better evidence on the serious risks of misuse and abuse associated with long-term opioid use, predictors of opioid addiction, and other important issues.
Prioritizing abuse-deterrent formulations and overdose treatments. Abuse-deterrent opioid formulations have the potential to reduce misuse of opioid medications, and broader access to naloxone may help mitigate harm from opioid overdose.	The FDA will continue to support abuse-deterrent formulations and, with guidance from an advisory committee, explore and encourage development of more effective abuse-deterrent features. The FDA will also prioritize issuance of draft guidance on generic abuse-deterrent opioids and will consider ways to make naloxone more widely available, including as an over-the-counter medication. In addition, new non–abuse-deterrent formulations submitted for FDA approval will also be reviewed by an advisory committee.
Addressing the lack of nonopioid alternatives for pain management. Although nonopioid medications for chronic pain have recently been approved for the market, more alternatives are needed, including nonpharmacologic treatments.	The FDA is working closely with industry and the National Institutes of Health to develop alternative medications without the addictive properties of opioids. Nonpharmacologic approaches to pain treatment have also been identified as an urgent priority.
Creating clear guidelines for opioid use. The current crisis in opioid misuse and abuse will continue unless prescribing physicians have a clear understanding of appropriate use and management.	The FDA is supporting the CDC's guideline for prescribing opioids for chronic pain control. The FDA also supports the Surgeon General's efforts to engage the clinical community in curbing inappropriate prescribing and proactively treating opioid addiction, while reinforcing evidence-based pain management approaches that spare the use of opioids.
Managing pain in children. Use of opioid medications in children with severe and chronic pain conditions requires special consideration, and physicians need information that helps them prescribe such medications safely and effectively, while protecting minors who lack mature decision-making capabilities.	An FDA Pediatric Advisory Committee will address the use of opioid medications in children, including the development of high-quality evidence to guide treatment, and provide input on the policies for adding new pediatric opioid labeling under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act before any new labeling is approved.
Developing a better evidence base. Despite ongoing efforts, the evidence base to guide the use of opioid medications, particularly in the setting of long-term use, is substantially lacking.	Health and Human Services agencies and the FDA program for mandated industry-funded studies are developing a coordinated plan for conducting research that will provide evidence to guide opioid use, elucidate the biologic phenomenon of pain, and consider new and alternative approaches to pain prevention and management.

HHS), the clinical and prescriber communities, and other stakeholders to ensure that all available effective tools are brought to bear on this epidemic and that the evidence base for proper pain management and appropriate opioid use is optimized and translated into practice.

BALANCING INDIVIDUAL AND SOCIETAL RISK

We will start by launching a broad reexamination of our approach, considering how best to apply existing policies to this problem, which policies need to be improved and updated, and whether new policies must be developed. Consideration of a range of risks that FDA-regulated products pose to their intended consumers and to others is important to our public health mission. In many cases, opioids can cause harm that goes beyond the risks to the person who has been prescribed the medicine, and inappropriate prescribing causes both direct and indirect harms that are difficult to track and measure but must be considered. We will therefore seek advice on how to more comprehensively take into account the risks of abuse for both patients and nonpatients when regulating these drugs.

We have asked the National Academy of Medicine (NAM) to help us develop a regulatory framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the broader public health consequences of abuse and misuse. Assessing the long-term risks of addiction and hyperalgesia (in which the use of opioids results in excess pain rather than pain relief), as well as other toxic effects and societal harm caused by diversion and related addiction, will require extrapolation from imperfect data. The NAM brings an unbiased and highly respected perspective on these issues that can help us revise our framework.

Since this intensive review will take time, we plan to pursue other activities and decisions in the interim. The evolving nature of the threat that opioid abuse poses to our country's health demands an approach in which we constantly consider available information, seek advice, and move forward, always ready to shift our actions as new information becomes available. Specifically, at its next meeting in March, the FDA's Science Board (comprising independent experts in regulatory science) will consider a series of relevant issues, aiming to advise the FDA on the role of pharmaceuticals in pain management, development of alternative pain medications, and postmarketing surveillance activities.

REVISITING OPIOID LABELING AND POSTMARKETING STUDY REQUIREMENTS

We will also reexamine how opioids should be labeled more generally. Current labeling for extended-release or long-acting (ER/LA) opioids, revised in September 2013, includes strict, detailed instructions requiring descriptions of their associated risks, the need for monitoring, and the facts that opioids should be used only when other measures are insufficient, the need to continue to use opioids should be reassessed regularly, and opioids should be dispensed in limited quantities.[3] In addition, manufacturers of ER/LA opioids will be required to conduct extensive postmarketing research (resulting in a total of 11 mandated studies), in order to study safety concerns that have been identified and evaluate methods to assess progress in mitigating them.

Manufacturers of ER/LA opioids are also subject to a Risk Evaluation and Mitigation Strategy (REMS)[4] program that requires them to fund continuing medical education (CME) providers to offer, at low or no cost, CME courses on the appropriate use of these products, subject to an online FDA curriculum. More than 38,000 prescribers have taken part in these voluntary educational programs, and an evaluation of these results is under way and will be considered by an advisory committee in the spring.

But although this voluntary training remains an important public health measure, the FDA continues to support mandatory education for prescribers, as called for in the 2011 Prescription Drug Abuse Prevention Plan[5] and reemphasized in the 2014 National Drug Control Strategy.[6] Together with other federal agencies and the clinical community, we should strive to overcome obstacles to enacting this measure. Along with improving prescriber education, we will assess whether broader measures should be instituted for labeling and postmarketing evaluation of the entire class of opioids.

DETERRING ABUSE AND MITIGATING HARM FROM OVERDOSE

In addition to the REMS approach to safety, the FDA has strongly supported the development and assessment of abuse-deterrent formulations

of opioids,[7] five of which the agency has already approved. The pharmaceutical industry has shown significant interest in developing abuse-deterrent opioid formulations and the field is progressing rapidly. The availability of abuse-deterrent formulations raises questions, including how to encourage their use in place of products without abuse-deterrent features and whether to modify criteria for the review and approval of oral opioid formulations that lack abuse-deterrent features or do not offer advantages in abuse deterrence relative to currently marketed products. We will continue to support abuse-deterrent formulations and encourage development of more effective abuse-deterrent features; we are also committed to convening advisory committees to consider new versions of non–abuse-deterrent opioids. In addition, draft FDA guidance on generic abuse-deterrent opioids will review many of the key issues; making this guidance available quickly is a high priority, since the availability of less costly generic products should accelerate prescribers' uptake of abuse-deterrent formulations. However, it is important to recognize that abuse-deterrent formulations by themselves when taken orally do not prevent the development of tolerance or addiction to opioids.

We have also strongly supported the development and marketing of countermeasures that can reverse overdose, such as the opioid antagonist naloxone. Rapid advances in the development and distribution of injectable and intranasal naloxone offer an example of an effort in which broad intersectoral collaboration has saved substantial numbers of people who would otherwise have died from overdose. The recent rapid approvals of intramuscular (via auto-injector)[8] and intranasal[9] naloxone were important steps in improving access to this lifesaving therapy. Are there ways to expand naloxone's availability? We will continue to explore expanding availability of naloxone in the coming year, including ways to make it available over the counter.

PRIORITIZING DEVELOPMENT OF NONOPIOID ALTERNATIVES FOR PAIN RELIEF

We are also working closely with industry and the National Institutes of Health to develop additional alternative medications that alleviate pain but do not have the addictive properties of opioids. Nonpharmacologic approaches to pain treatment are also an urgent priority. The FDA has approved nonopioid medications for treatment of various chronic-pain syndromes, including gabapentin (Neurontin), pregabalin (Lyrica), milnacipran (Savella), duloxetine (Cymbalta), and others, and a number of promising development programs are in the pipeline. But we need more. The FDA will use all the tools at its disposal to move these alternatives along as expeditiously as possible, while remaining mindful that all medicines have risks. For example, although nonsteroidal antiinflammatory drugs do not carry a risk of addiction, we now know that they carry increased risks of myocardial infarction, stroke, and serious gastrointestinal bleeding.

REFINING GUIDELINES FOR OPIOID USE

A comprehensive solution to the current opioid crisis goes well beyond the FDA's remit. However, thanks to our access to rich data sources and the broader federal effort to define the issues, we are in a position to see the problems that medical practice and public health must confront and to provide guidance in addressing them. Accordingly, we are supporting the CDC's Guideline for Prescribing Opioids for Chronic Pain. The draft guideline[10] received extensive public comment, and we look forward to participating in the process when the CDC finalizes it soon. We are also supporting the Surgeon General's efforts[11] to engage the clinical community in a concerted approach to curbing inappropriate prescribing and proactively treating opioid addiction, while reinforcing evidence-based approaches to treating pain in a manner that spares the use of opioids. Until clinicians stop prescribing opioids far in excess of clinical need, this crisis will continue unabated.

MANAGING PAIN IN CHILDREN

The care of children with debilitating pain for whom other measures do not bring comfort deserves particular consideration. Recent labeling changes for oxycodone (OxyContin) that provided evidence-based dosing information for pediatric use created substantial controversy.

Children who are prescribed oxycodone or other opioids have severe conditions that include cancer, multisystem trauma, and serious chronic diseases such as sickle cell anemia or have undergone multiple surgical procedures. We must care for our most vulnerable patients, but we must also do everything possible to avoid both the inappropriate prescribing of powerful opioid medications and the misuse of these prescriptions.

When Congress enacted the Pediatric Research Equity Act, it enabled the FDA to require industry to conduct studies to determine the appropriate dosing of medications in children; the Best Pharmaceuticals for Children Act provided incentives for performing these studies for products that were already approved.[12] For children whose circumstances require treatment with opioids, we will consider how best to ensure that doctors get the information they need to prescribe such medications safely and effectively, while protecting minors who lack mature decision-making capabilities.

As physicians and regulators — and as parents — we know that we must treat pain in a suffering child. But in some cases, children with serious conditions are being treated with opioids in the absence of adequate knowledge about correct indications and dosing. We must all work together to ensure that all appropriate therapeutic options for pain are available to children, but it is equally important that when opioids are used, they are prescribed and handled in an impeccably judicious manner, guided by the best and most current scientific evidence. To this end, we are convening the Pediatric Advisory Committee on two upcoming occasions in order to specifically address issues related to the use of opioid medications in children, including the development of high-quality evidence to guide treatment, pediatric labeling for opioids, and improving practice to reduce addiction, misuse, and diversion.

The committee will consider appropriate approaches for ensuring that clinicians have ready access to reliable dosing information and will recommend methods for ensuring that clinicians scrupulously follow the regulations and best practices governing the use of such medications.

DEVELOPING A BETTER EVIDENCE BASE FOR CHRONIC PAIN TREATMENT

The FDA does its best work when high-quality scientific evidence is available to assess the risks and benefits of intended uses of medical products. Unfortunately, the field of chronic pain treatment is strikingly deficient in such evidence. A key lesson learned during the development of the CDC guideline is that there is very little research on the long-term benefits of opioids for treating chronic pain. There is, however, growing evidence of harms associated with such use, and of the benefits of other nonopioid treatment alternatives. As with all clinical guidelines, continued research is needed to inform clinical practice. But given the severity of the crisis, the draft CDC guideline provides a highly reasonable set of recommendations for primary care providers to use in their clinical practices, allowing physicians and patients together to determine treatment plans on the basis of the best current understanding of risks and benefits.

Recognition of this problem led the FDA, several years ago, to require industry to perform a series of studies on questions that are critical for ensuring safe prescribing.[4] For example, until recently it was believed that opioids' pain-relieving properties would not be time-dependent, but new studies have raised the question of whether opioids continue to be effective or may even increase pain in some patients after several months of use. To explore this question, 1 of the 11 postmarketing studies the FDA is requiring industry to fund is a clinical trial in which participants are randomly assigned to continue opioid therapy or to be weaned from it on a schedule over the course of 1 year of follow-up.

As policies are implemented and new evidence is generated, we will continuously assess findings and ensure that the agency's proposed strategies are evaluated in the context of new data. By implementing a coordinated effort among public and private partners, we will be able to adapt our strategies as the evidence base improves. We are committed to this renewed effort and believe that by working together we can solve the opioid crisis, while gaining ground in the national effort to prevent and control short-term and chronic pain.

Nationally, the annual number of deaths from opioid overdoses now exceeds the number of deaths caused by motor vehicle accidents.[13] Regardless of whether we view these issues from the perspective of patients, physicians, or regulators, the status quo is clearly not acceptable. As the public health agency responsible for oversight of pharmaceutical safety and effectiveness, we recognize that this crisis demands solutions. We are committed to action, and we urge others to join us.

Dr. Califf reports receiving consulting fees from Amgen, Bayer Healthcare, BMEB Services, Bristol-Myers Squibb, Janssen, Medscape/Heart.org, Merck, Novartis, Regado, Roche, AstraZeneca, Genentech, GlaxoSmithKline, Heart.org/Daiichi-Sankyo, Kowa, Servier, Bayer Pharma, CV Sight, DSI-Lilly, Gambro, Gilead Sciences, Heart.org/Bayer, Pfizer, Regeneron, the Medicines Company, Nile, and Parkview; receiving grant support from Amylin, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novartis, the Schering-Plough Research Institute, Scios, and Parkview; and holding equity in Nitrox/N30 Pharma and Portola, all prior to March 1, 2015. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Food and Drug Administration, Silver Spring, MD.

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COMPLAINT

EXHIBIT #13

CDC Press Release

November 1, 2011

Press Release

For Immediate Release: November 1, 2011
Contact: CDC Online Newsroom
(404) 639-3286

Prescription painkiller overdoses at epidemic levels

Kill more Americans than heroin and cocaine combined

The death toll from overdoses of prescription painkillers has more than tripled in the past decade, according to an analysis in the CDC Vital Signs report released today from the Centers for Disease Control and Prevention. This new finding shows that more than 40 people die every day from overdoses involving narcotic pain relievers like hydrocodone (Vicodin), methadone, oxycodone (OxyContin), and oxymorphone (Opana).

"Overdoses involving prescription painkillers are at epidemic levels and now kill more Americans than heroin and cocaine combined, " said CDC Director Thomas Frieden, M.D., M.P.H. "States, health insurers, health care providers and individuals have critical roles to play in the national effort to stop this epidemic of overdoses while we protect patients who need prescriptions to control pain. "

The increased use of prescription painkillers for nonmedical reasons (without a prescription for the high they cause), along with growing sales, has contributed to the large number of overdoses and deaths. In 2010, 1 in every 20 people in the United States age 12 and older—a total of 12 million people—reported using prescription painkillers nonmedically according to the National Survey on Drug Use and Health. Based on the data from the Drug Enforcement Administration, sales of these drugs to pharmacies and health care providers have increased by more than 300 percent since 1999.

"Prescription drug abuse is a silent epidemic that is stealing thousands of lives and tearing apart communities and families across America, " said Gil Kerlikowske, Director of National Drug Control Policy. "From day one, we have been laser–focused on this crisis by taking a comprehensive public health and public safety approach. All of us have a role to play. Health care providers and patients should be educated on the risks of prescription painkillers. And parents and grandparents can take time today to properly dispose of any unneeded or expired medications from the home and to talk to their kids about the misuse and abuse of prescription drugs. "

In April, the Administration released a comprehensive action plan to address the national prescription drug abuse epidemic to reduce this public health burden.

Titled "Epidemic: Responding to America's Prescription Drug Abuse Crisis, " the plan includes support for the expansion of state–based prescription drug monitoring programs, more convenient and environmentally responsible disposal methods to remove unused medications from the home, education for patients and healthcare providers, and support for law enforcement efforts that reduce the prevalence of "pill mills" and doctor shopping.

Already, 48 states have implemented state–based monitoring programs designed to reduce diversion and doctor shopping while protecting patient privacy and the Department of Justice has conducted a series of takedowns of rogue pain clinics operating as "pill mills." President Obama has also signed into law the Secure and Responsible Drug Disposal Act, which will allow states and local communities to collect and safely dispose of unwanted prescription drugs and support DEA's ongoing national efforts to collect unneeded or expired prescription drugs which have collected over 300 tons of medications over the past year.

"Almost 5,500 people start to misuse prescription painkillers every day," said Substance Abuse and Mental Health Services Administration Administrator Pamela S. Hyde. "Just like other public health epidemics, community–based prevention can be a proven, life–saving and cost–effective key to breaking the trend and restoring health and well–being."

The prescription painkiller death rates among non–Hispanic whites and American Indians/Alaska Natives were three times those of blacks and Hispanic whites. In addition, the death rate was highest among persons aged 35–54 years. Overdose resulted in 830,652 years of potential life lost before age 65 years, a number comparable to the years of potential life lost from motor vehicle crashes and much higher than the years of potential life lost due to homicide.

For the analysis, CDC reviewed state data on fatal drug overdoses, nonmedical use of prescription painkillers, and sales of prescription painkillers to pharmacies and health care providers.

The study found:

- State death rates from overdoses (from 2008 data) ranged from a high of 27.0 deaths per 100,000 people in New Mexico to a low of 5.5 deaths per 100,000 people in Nebraska.
- Nonmedical use of prescription painkillers ranged from a high of 1 in 12 people aged 12 and older in Oklahoma to a low of 1 in 30 in Nebraska. States with more nonmedical use tend to have more deaths from drug overdoses.
- Prescription painkiller sales per person were more than three times higher in the highest state, Florida, than in the lowest state, Illinois. States with higher sales per person tend to have higher death rates from drug overdose.

While national strategies are being strengthened, states, as regulators of health care practice and large public insurers, can take the following steps to help prevent overdoses from prescription painkillers and reduce this public health burden:

- Start or improve prescription drug monitoring programs, which are electronic databases that track all prescriptions for painkillers in the state.
- Use prescription drug monitoring programs, public insurance programs, and workers' compensation data to identify improper prescribing of painkillers.
- Set up programs for public insurance programs, workers' compensation programs, and state–run health plans that identify and address improper patient use of painkillers.
- Pass, enforce and evaluate pill mill, doctor shopping and other state laws to reduce prescription painkiller abuse.
- Encourage professional state licensing boards to take action against inappropriate prescribing.
- Increase access to substance abuse treatment.

CDC is also releasing "Policy Impact: Prescription Painkiller Overdoses," one in a series of issue briefs highlighting key public health issues and important, science–based policy actions that can be taken to address them. Through this new publication, CDC supports state–based efforts to reduce prescription drug abuse while ensuring patients have access to safe, effective pain treatment.

For more information about prescription drug overdoses in the United States, please visit www.cdc.gov/HomeandRecreationalSafety/Poisoning.

CDC works 24/7 saving lives, protecting people from health threats, and saving money to have a more secure nation. Whether these threats are chronic or acute, manmade or natural, human error or deliberate attack, global or domestic, CDC is the U.S. health protection agency.

Vital Signs is a CDC report that appears on the first Tuesday of the month as part of the CDC journal Morbidity and Mortality Weekly Report, or MMWR. The report provides the latest data and information on key health indicators, such as cancer prevention, obesity, tobacco use, motor vehicle passenger safety, prescription drug overdose, HIV/AIDS, alcohol use, health care–associated infections, cardiovascular health, teen pregnancy, asthma, and food safety.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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COMPLAINT

EXHIBIT #14

Dart NEJM

January 15, 2015

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Trends in Opioid Analgesic Abuse and Mortality in the United States

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ABSTRACT

BACKGROUND

The use of prescription opioid medications has increased greatly in the United States during the past two decades; in 2010, there were 16,651 opioid-related deaths. In response, hundreds of federal, state, and local interventions have been implemented. We describe trends in the diversion and abuse of prescription opioid analgesics using data through 2013.

METHODS

We used five programs from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System to describe trends between 2002 and 2013 in the diversion and abuse of all products and formulations of six prescription opioid analgesics: oxycodone, hydrocodone, hydromorphone, fentanyl, morphine, and tramadol. The programs gather data from drug-diversion investigators, poison centers, substance-abuse treatment centers, and college students.

RESULTS

Prescriptions for opioid analgesics increased substantially from 2002 through 2010 in the United States but then decreased slightly from 2011 through 2013. In general, RADARS System programs reported large increases in the rates of opioid diversion and abuse from 2002 to 2010, but then the rates flattened or decreased from 2011 through 2013. The rate of opioid-related deaths rose and fell in a similar pattern. Reported nonmedical use did not change significantly among college students.

CONCLUSIONS

Postmarketing surveillance indicates that the diversion and abuse of prescription opioid medications increased between 2002 and 2010 and plateaued or decreased between 2011 and 2013. These findings suggest that the United States may be making progress in controlling the abuse of opioid analgesics. (Funded by the Denver Health and Hospital Authority.)

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Whatever the measure, the past two decades have been characterized by increasing abuse and diversion of prescription drugs, including opioid medications, in the United States. An estimated 25 million people initiated nonmedical use of pain relievers between 2002 and 2011.[1] The number of deaths per year attributed to prescription opioid medications reached 16,651 in 2010.[2] In response to the epidemic, hundreds of local, regional, state, and federal interventions have been implemented. For example, 49 states have enacted legislation to create prescription-drug monitoring programs.[3] The U.S. Office of National Drug Control Policy has responded to the epidemic with numerous recommendations, including the need to evaluate "current databases that measure the extent of prescription drug use, misuse, and toxicity."[4] In 2013, a Pew Research Center survey showed that only 16% of Americans believed that the United States was making progress in reducing prescription-drug abuse.[5]

The impressive response to the epidemic is heartening, but the effect of these programs is not yet known. Some local and state interventions have described a reduction in the abuse and diversion of prescription opioids after the enactment of state legislation.[6,7] We used the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System to describe the diversion and abuse of prescription opioid analgesics, using data from January 2002 through December 2013. Because drug abuse is an illegal activity that is often concealed from authorities, the RADARS System uses a "mosaic" approach, measuring abuse and diversion from multiple perspectives, to describe this hidden phenomenon as comprehensively as possible.[8]

METHODS

DATA SOURCES AND OVERSIGHT

We used data from five separate RADARS System programs (Table 1). The Poison Center Program records the substances involved in poison-center cases classified as intentional abuse. The Drug Diversion Program records the drugs involved in cases opened by law-enforcement agencies investigating prescription-drug diversion. The Opioid Treatment Program and the Survey of Key Informants' Patients (SKIP) Program query new patients entering substance-abuse treatment about medications that they have abused in the previous 30 days. The College Survey Program is a Web-based survey in which self-identified college students report their nonmedical use of prescription drugs during the previous 30 days. Further information on each program is provided in Table 1, the Supplementary Appendix (available with the full text of this article at NEJM.org), and previous publications.[9-13] Several analyses describe the relations among these programs and other information sources such as the Drug Abuse Warning Network and the National Vital Statistics System.[10,14]

To represent the trends with respect to prescription opioid analgesics, we grouped all marketed products and formulations (branded and generic) of six prescription analgesics: oxycodone, hydrocodone, hydromorphone, fentanyl, morphine, and tramadol. More recent market entrants with smaller market shares (e.g., oxymorphone and tapentadol) were excluded so that the trend analysis involved a consistent profile of analgesics. Sensitivity analyses showed that the results were not materially affected by the exclusion of these products. In addition, we retrieved data on reported heroin use in the past 30 days in the Opioid Treatment, SKIP, and College Survey Programs. (Not all programs include heroin because the RADARS System focuses on prescription opioids.) Because the RADARS Poison Center Program does not collect data on heroin, we obtained counts of heroin-related cases from the National Poison Data System (American Association of Poison Control Centers) and data on reported heroin use in the past 30 days (National Survey on Drug Use and Health).[15,16] Data on prescription volume were obtained from IMS Health.[17]

The RADARS System is independently owned and operated by the Denver Health and Hospital Authority, which operates the public hospital for the city and county of Denver. The system is supported by subscriptions from pharmaceutical companies that produce prescription opioids or stimulants, which use the data for risk management and postmarketing surveillance reporting to the Food and Drug Administration. Subscribers had no role in the conception, execution, or reporting of this analysis. Each program in the RADARS System is approved by the institutional review board of the principal investigator's institution (Tables S1 through S6 in the Supplementary Appendix).

STATISTICAL ANALYSIS

We plotted the quarterly event rate by dividing the total number of events for the prescription-opioid group for each program by the population of the jurisdiction or coverage area of the program. Population data were obtained from the 2000 and 2010 U.S. Census at the level of the three-digit ZIP Code. Interpolation and extrapolation at this level adjusted for population changes over time. Because the plots were suggestive of a second-degree polynomial fit, we used a Poisson regression model with linear and quadratic terms for time. Quadratic and cubic models were evaluated, and the quadratic model was chosen because it fit the largest number of programs. We computed the time of the maximum predicted value (vertex) of the curve, which indicates when the population rate changed from an increasing to a decreasing trajectory. A negative quadratic coefficient indicates that the quadratic curve is concave (with the apex at the top and the curve opening downward). The t-statistic was used to test whether the quadratic coefficient differed from zero. A significant result indicates that the quadratic term provided a better fit to the data than the linear term.

RESULTS

TRENDS IN OPIOID ANALGESIC USE

Prescription data from IMS Health indicate that at the beginning of 2006, there were 47 million prescriptions dispensed per quarter in the United States for the opioid analgesics included in this study. Prescription volume peaked in the fourth quarter of 2012 at 62 million prescriptions dispensed. Except for this one quarter, the number of prescriptions trended slightly downward from 2011 through 2013, ending at 60 million prescriptions per calendar quarter for study medications (Fig. 1A).

In the Drug Diversion Program, the calculated quarterly event rate for prescription opioids increased from approximately 1.5 per 100,000 population in 2002 to 2.9 in 2012 and then decreased to 2.5 by the end of 2013 (Fig. 1B). In the Poison Center Program, the quarterly abuse rate for opioid analgesics increased from 0.20 per 100,000 population in 2003 to 0.56 in 2010 and then decreased to 0.35 by the end of 2013 (Fig. 1C). In the Opioid Treatment Program, the rate of prescription opioid abuse increased from

Table 1. Description of Surveillance Programs in the RADARS System.*

Program	Definition of Event	Respondent	Program Coverage	Data Collection	No. of Events Involving Opioid Analgesic and Corresponding Drug Mentions
Drug Diversion	Written complaint or report	Law-enforcement agencies	260 drug-diversion respondents in 49 states, with jurisdictions covering 38.1% of U.S. population	Standardized report	145,090 cases involving 146,786 opioid analgesic mentions, 2002–2013
Poison Center	Person choosing to contact a poison center	Patient, acquaintance, or health care professional	49 regional U.S. poison centers in 46 states (91.5% of total U.S. population)	Electronic medical record	456,610 cases involving 491,874 opioid analgesic mentions, 2003–2013
Opioid Treatment	Reported use of drugs to get "high"	Patient entering substance-abuse treatment program	66 programs in 34 states	Standardized questionnaire on admission	41,031 cases involving 183,573 opioid analgesic mentions, 2005–2013
Survey of Key Informants' Patients	Reported use of drugs to get "high"	Patient entering substance-abuse treatment program	109 programs in 45 states	Standardized questionnaire on admission	10,214 cases involving 64,678 opioid analgesic mentions, 2008–2013
College Survey	Reported nonmedical use of prescription drugs	Self-identified college students	2000 students each term (spring, summer, and fall)	Web-based survey	3564 cases involving 11,871 opioid analgesic mentions, 2008–2013

* RADARS denotes Researched Abuse, Diversion, and Addiction-Related Surveillance.

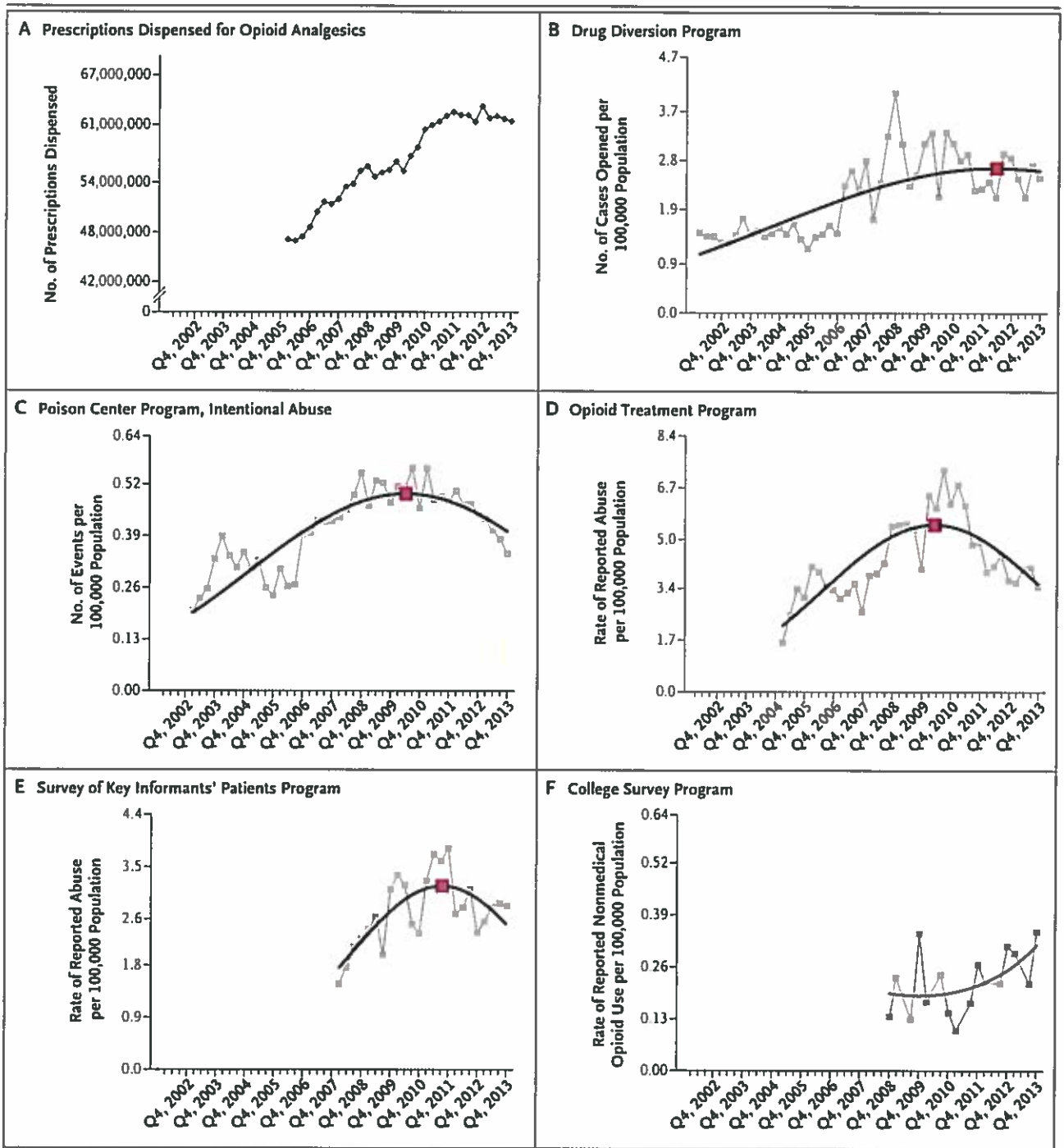

Figure 1. Prescriptions Dispensed for Opioid Analgesics and Rates of Abuse and Diversion, RADARS System, 2002–2013.

Data are displayed according to calendar quarter. Panel A shows the number of prescriptions dispensed for the opioid analgesics included in the analysis (IMS Health). Panel B shows the rate of drug-diversion cases opened. Panel C shows the rate of cases of intentional abuse reported to participating poison centers. Panel D shows the rate of reported abuse by persons entering methadone programs. Panel E shows the rate of reported abuse by patients entering other substance-abuse treatment programs. Panel F shows the rate of reported nonmedical opioid use by college students. The red boxes in Panels B through E indicate the vertex of the quadratic curve. (There is no red box in Panel F because the quadratic terms were not significant; Panel A is provided for context and was not part of the planned analysis.) Details of the data-collection procedure and case definition are provided in the Supplementary Appendix. RADARS denotes Researched Abuse, Diversion, and Addiction-Related Surveillance.

1.6 per 100,000 population in 2005 to 7.3 in 2010 and then decreased to 3.5 by the end of 2013 (Fig. 1D). In the SKIP Program, the rate of prescription opioid abuse increased from 1.5 per 100,000 population in 2008 to 3.8 in 2011 and then decreased to 2.8 by the end of 2013 (Fig. 1E). In the College Survey Program, the rate of nonmedical use increased from 0.14 per 100,000 population in 2008 to 0.35 by the end of 2013 (Fig. 1F). Using a Poisson regression model, we found that the quadratic coefficient was negative and significantly different from zero in the Poison Center Program ($P<0.001$), the Drug Diversion Program ($P=0.009$), the Opioid Treatment Program ($P<0.001$), and the SKIP Program ($P=0.001$). Before mid-2010, the rate of diversion or abuse was increasing in each program; however, the rate in each program trended downward by 2013. The only exception was the College Survey Program, in which the quadratic term was not significant ($P=0.41$).

Reported heroin use generally increased over time. In poison centers, as evidenced by data from the National Poison Data System, the rate of heroin-related cases started increasing in 2006 and appeared to accelerate in late 2010 (Fig. 2A). In conjunction with increasing heroin use, cases involving the extended-release formulation of oxycodone (OxyContin, Purdue Pharma) decreased substantially after the introduction of an abuse-deterrent formulation (Fig. 2A). In the Opioid Treatment Program, the rate of heroin use was flat for the period from 2005 through 2013, and the rate of abuse of reformulated extended-release oxycodone decreased after 2010 (Fig. 2B). In the SKIP Program, the rate of heroin use increased in 2011 and remained increased, whereas the rate of abuse of reformulated extended-release oxycodone decreased (Fig. 2C). In the College Survey Program, the rate of heroin use was volatile but generally flat, whereas the rate of abuse of reformulated extended-release oxycodone edged upward (Fig. 2D). Reported use of heroin increased after 2005 in the National Survey on Drug Use and Health (Fig. 2E).

OPIOID-RELATED DEATHS

The rate of death associated with heroin use (data from the National Poison Data System) was inversely related to the rate of death associated with the use of prescription opioid drugs. The rate of opioid-related death increased from 2002 to 2006, plateaued from 2006 through 2008, then decreased slightly from 2009 through 2013 (Fig. 3). In contrast, the rate of heroin-related death was flat from 2002 to 2010 but increased each subsequent year through 2013.

DISCUSSION

Our results show a parallel relationship between the availability of prescription opioid analgesics through legitimate pharmacy channels and the diversion and abuse of these drugs and associated adverse outcomes. Availability increased greatly in the 1990s and continued through 2010 but then plateaued from 2011 through 2013. In concert with these findings, four of five RADARS System surveillance programs reported large increases in diversion and abuse from 2002 to 2010. An inflection point was reached in each program, however, and the rates of diversion and abuse of prescription analgesics subsequently decreased.

For the period before 2011, our results are similar to those in other research reports, with increasing rates of opioid analgesic abuse. The Drug Abuse Warning Network reported an increase of 183% in medical emergencies related to opioid pharmaceuticals from 2004 to 2011, the last year for which data are available.[18] The National Survey on Drug Use and Health noted increasing dependence on and abuse of prescription pain relievers from 2002 through 2012, the last year for which data are available.[19] Similarly, admissions for the treatment of opioid dependence and addiction increased through 2011.[20] These increases in drug availability and abuse have been reflected in the numbers of deaths caused by prescription opioids, which increased for 11 consecutive years and reached 16,651 deaths nationally in 2010.[2]

Few data regarding national trends in prescription-drug abuse and diversion since 2010 have been published. However, emerging data suggest that abuse of prescription opioids may have lessened in some environments. For example, local and state efforts have resulted in a reduction after the enactment of state legislation.[6] Florida had a substantial decrease in the diversion of prescription analgesics, especially oxycodone, after several interventions were implemented in 2010 and 2011.[7] Reported prescription-drug abuse was also reduced in a study

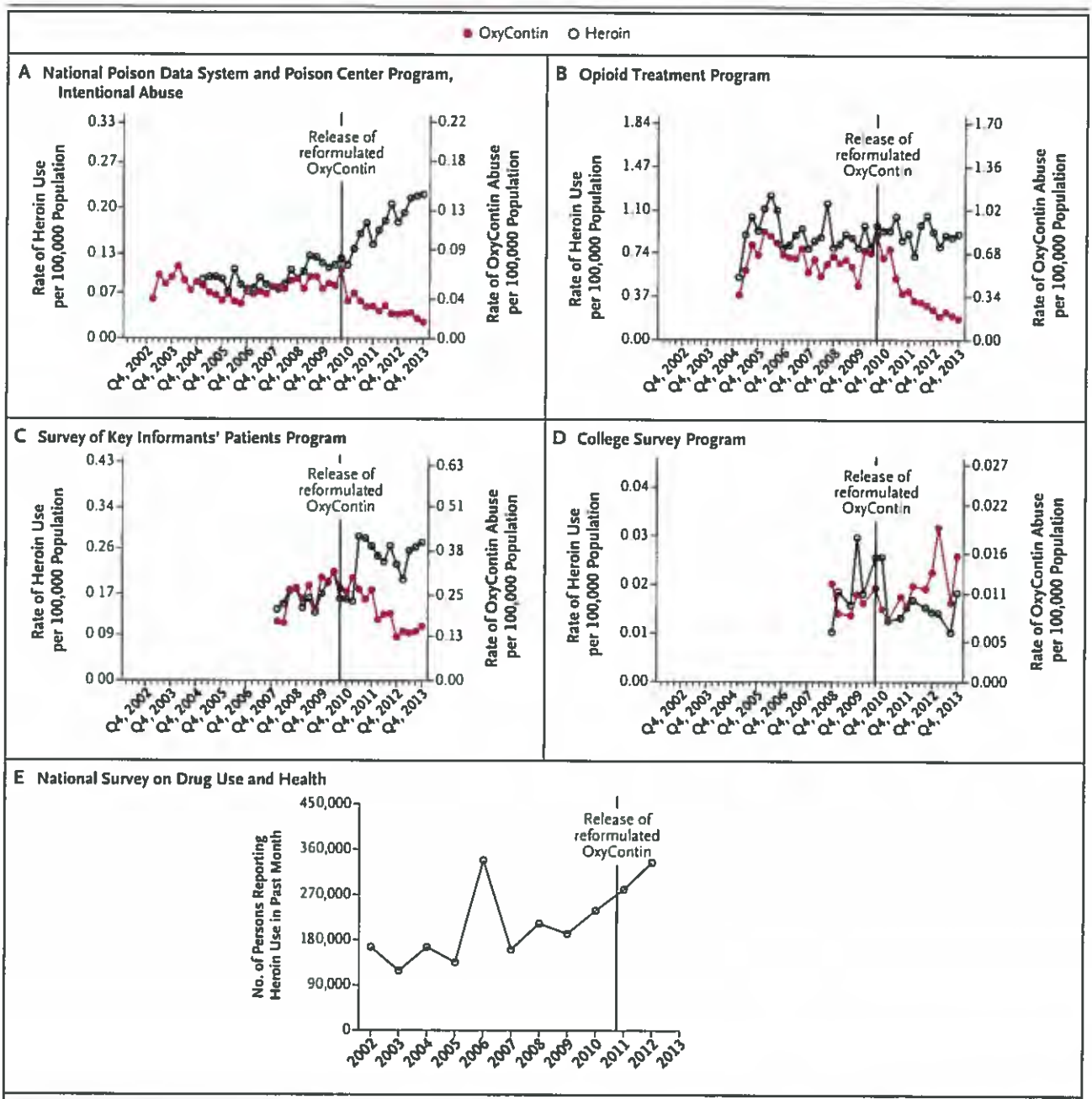

Figure 2. Rates of Heroin Use and OxyContin Abuse before and after OxyContin Reformulation.

Data are displayed according to calendar quarter and in relation to the release of reformulated OxyContin in August 2010 (vertical line in each panel). Panel A shows data for heroin use (National Poison Data System, American Association of Poison Control Centers) and intentional abuse of OxyContin (RADARS Poison Center Program). Panel B shows the rate of reported heroin use and OxyContin abuse by patients entering the RADARS Opioid Treatment Program. Panel C shows the rate of reported heroin use and OxyContin abuse by patients entering the RADARS Survey of Key Informants' Patients Program. Panel D shows the rate of reported heroin use and OxyContin abuse in the RADARS College Survey Program. Panel E shows the rate of reported heroin use in the National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration).

involving college students.[21] In contrast, the prevalence of nonmedical use of prescription analgesics remained unchanged in the National Survey on Drug Use and Health through 2012.[19]

The observed trends in opioid analgesic abuse could be related to several factors. The flattening rate of prescription volume since 2011 may have limited the availability of prescription opi-

oids for abuse. This trend may be evidence of either a decreased supply, because prescribers have reduced the number of prescriptions that they write, or a decreased demand, because the number of patients requesting these drugs has decreased. Although it may be assumed that the prescribers control the supply of a drug, the supply is influenced by persons who feign a painful illness to acquire a prescription. A decrease in requests by these persons will result in a decrease in the number of prescriptions filled. For example, studies show that the introduction of a less desirable formulation of oxycodone can rapidly decrease demand for that formulation.[22]

Another explanation involves the hundreds of programs implemented by local, state, and federal governments to improve opioid prescribing, reduce doctor-shopping, limit questionable practices by pain clinics, and otherwise improve the use of opioid analgesics in the United States.[3] In addition, other organizations have implemented myriad programs such as guidelines for responsible opioid prescribing and educational initiatives designed to decrease experimentation. Prescription-monitoring programs now operate in most states, and early studies indicate their effectiveness.[23,24] New opioid analgesic formulations that resist tampering have been introduced. Finally, law enforcement has intervened successfully in some cases, such as closing so-called pill mills in Florida.[7] It seems plausible that these efforts have started to take effect.

The role of switching from the abuse of a prescription opioid to the use of high-purity, low-cost heroin must also be considered.[25] Our results support this explanation, as do results from the National Survey on Drug Use and Health, in which reported use of heroin in the previous month increased from 2006 to 2012 (Fig. 2E).[19] The introduction of abuse-deterrent OxyContin coincided with a flattening of the trajectory of opioid analgesic prescriptions but occurred after the increase in reported heroin use became apparent. Given that 79.5% of new heroin initiates in the National Survey on Drug Use and Health reported that their initial drug was a prescription opioid and that reported heroin use by patients in a substance-abuse program nearly doubled after the introduction of abuse-deterrent OxyContin, it seems likely that the reformulation of extended-release oxycodone in 2010 has contributed to the increase in reported heroin use.[26,27]

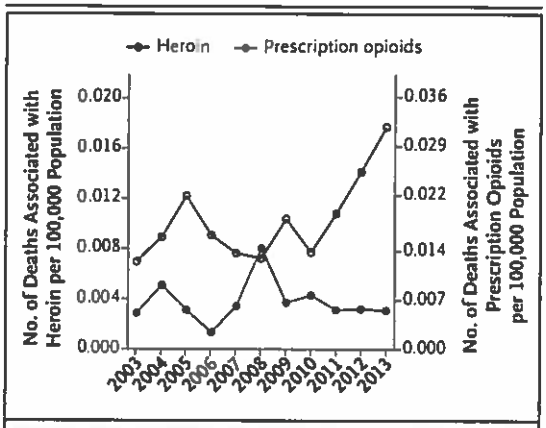

Figure 3. Rates of Death Associated with Heroin and Prescription Opioids, 2002–2013.

Shown is the rate of death associated with prescription opioid drugs (RADARS Poison Center Program) and with heroin (National Poison Data System, American Association of Poison Control Centers), with adjustment for population.

Whatever the precise cause, changes in rates of opioid analgesic abuse are associated with increasing heroin-related mortality. The similarities between data from the National Survey on Drug Use and Health and data from the National Poison Data System with respect to heroin use and adverse consequences are striking (Fig. 2A and 2E, and Fig. 3). A better understanding of the relation between prescription opioid abuse and heroin use is crucial for developing public health policy as well as guiding prevention and treatment initiatives.

The largest threat to the validity of our results is secular change in the study populations. Another concern is methodologic idiosyncrasy resulting in a systematic bias toward reduced diversion and abuse. We believe these explanations for our findings are unlikely because each RADARS program is operated independently by separate principal investigators and each addresses a different aspect of drug abuse. The data source, methods, and data management are different for each program. We cannot identify any programmatic changes that would have created an artifactual decrease in reported opioid use. Further limitations are described in the Supplementary Appendix.

Our results suggest that the United States is making progress in combating the abuse of prescription opioid analgesics. If our observa-

tion of decreased abuse is confirmed, changes in public health policy and strategy will be needed.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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COMPLAINT

EXHIBIT #15

Keyes AMJH

February 2014

Understanding the Rural–Urban Differences in Nonmedical Prescription Opioid Use and Abuse in the United States

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Nonmedical prescription opioid misuse remains a growing public problem in need of action and is concentrated in areas of US states with large rural populations such as Kentucky, West Virginia, Alaska, and Oklahoma. We developed hypotheses regarding the influence of 4 factors: (1) greater opioid prescription in rural areas, creating availability from which illegal markets can arise; (2) an out-migration of young adults; (3) greater rural social and kinship network connections, which may facilitate drug diversion and distribution; and (4) economic stressors that may create vulnerability to drug use more generally. A systematic consideration of the contexts that create differences in availability, access, and preferences is critical to understanding how drug use context varies across geography. (*Am J Public Health*. 2014;104:e52–e59. doi:10.2105/AJPH.2013.301709)

Nonmedical prescription opioid use is a rapidly escalating public health problem. Unintentional overdose deaths from opioid pain relievers has quadrupled since 1999 and by 2007 outnumbered those involving heroin and cocaine combined.[1] Much of this growth has been because of an increased misuse of opioid analgesics, which contributed to 21% of all poisoning deaths in 1999 and 37% in 2006.[2] By 2010, 2.4 million Americans initiated nonmedical prescription opioid use; this equals 6600 daily initiates.[3] Other evidence demonstrates a sharp increase in rates of use of prescription opioids[4,5] abuse or dependence,[4] emergency department visits,[6,7] and overdose injury among all age groups in the United States.[8–10]

Although all states have demonstrated an increase in nonmedical prescription opioid morbidity and mortality during the past decade, death and injury from nonmedical prescription opioid misuse are concentrated in states with large rural populations, such as Kentucky, West Virginia, Alaska, and Oklahoma.[11–13] Distinctions between urban and rural areas are not binary but reflect a continuum of population density and proximity to the 1098 defined metropolitan areas of the United States.[14] We conceptualized rural areas as nonmetropolitan counties, acknowledging that this is a heterogeneous category for geographical areas.

Individuals in counties outside metropolitan areas have higher rates of drug poisoning deaths, including deaths from opioids, and opioid poisonings in nonmetropolitan counties have increased at a rate greater than threefold the increase in metropolitan counties.[11] Drug-related deaths involving opioid analgesics are higher in these rural areas even after adjusting for population density,[15] and the ratio of nonmedical users to medical users is higher in rural areas as well.[16] Nationally representative surveys have indicated that, in rural areas, not only are there higher mortality and injury rates but also adolescents are more likely to use prescription opioids nonmedically than are their urban counterparts.[17–20] These surveys also report that factors such as polydrug use and depression are associated with nonmedical opioid use in rural areas.[20]

Why is nonmedical prescription opioid misuse more prevalent in rural areas than in urban areas? There is, surprisingly, little empirical data that help us address this question. Risk factors that explain rural–urban differences in nonmedical prescription opioid use must vary across rural versus urban geographical contexts and be either associated with drug use generally or use of nonmedical prescription opioids specifically. Although contextual determinants of drug use are important in explaining why individuals use drugs and become dependent,[21,22] our understanding of the mechanisms through which broadly defined geographical settings influence drug use remains limited.

We approached this issue in 3 steps. First, we explicated an array of known risk factors associated with illicit drug use generally. Second, we considered whether any of these factors are associated specifically with nonmedical prescription opioid use. Third, we linked the factors to the rural context, providing hypotheses that may explain the excess burden of prescription opioid misuse in rural compared with urban areas.

RISK FACTORS THAT DRIVE ILLICIT DRUG USE

Our model of drug use risk factors is grounded in ecosocial theory and ecological systems theory[21,23,24] and is organized by 3 levels of influence that dynamically interact (Figure 1).

The first is the macro level, where the social context structures the availability of drugs and the norms around use.[25,26] Furthermore, stressors at a macro level such as economic deprivation,[27] inequality,[28] structural discrimination,[29] and other pervasive stressors in the environment may serve as risk factors for drug use.[30,31]

The second is the local context, which includes family dynamics (e.g., supervision, conflict),[32–35] family composition (e.g., older siblings),[36] and family stress (e.g., unemployment). Furthermore, peer influence is a strong correlate of drug use.[37,38]

The third is the micro level. Endogenous factors such as genetic vulnerability,[39] neurobiological factors,[40–42] pharmacological reactivity,[43] personality traits such as sensation seeking and impulsivity,[44,45] psychiatric morbidity,[46–48] and gender and age[49,50] have strong and substantial influences on the propensity to misuse drugs and develop chronic

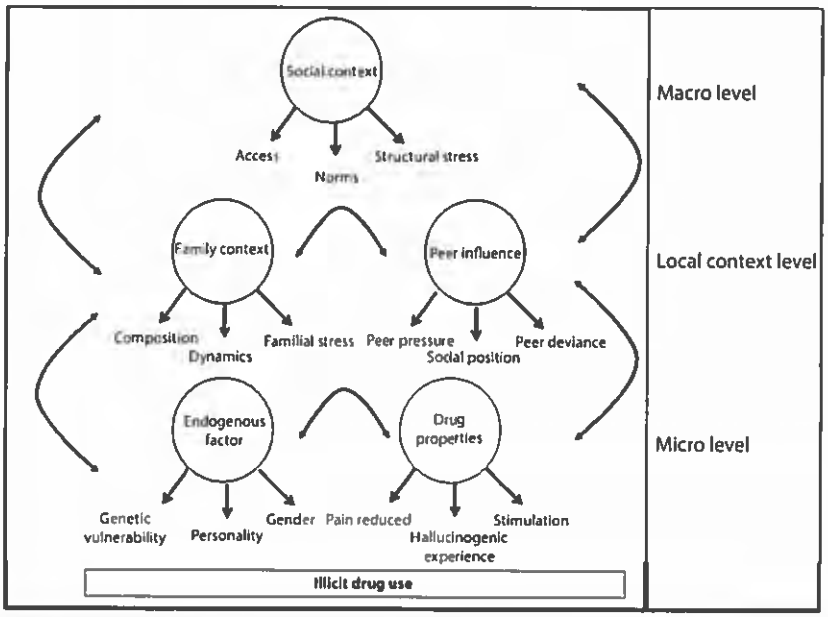

FIGURE 1—A conceptual framework for the etiology of illicit drug use.

drug dependencies. The pharmacological properties of a drug are important in determining who uses them and how they use them.[22]

These 3 levels of influence interact in dynamic ways; for example, social norms regarding substance use, a contextual influence, may affect how peers interact and form relationships around substance use.[51]

NONMEDICAL PRESCRIPTION DRUGS VS OTHER ILLICIT DRUGS

Many of the well-documented risk factors for illicit drug use predict both nonmedical prescription opioid use and other illicit drug use. Therefore, these cannot readily explain why nonmedical prescription opioid use is increasing, especially in rural areas. For example, nonmedical prescription drug users are more likely to be male,[52,53] be young,[54] be polydrug users,[55] have comorbid psychopathology,[54,56–59] and have positive expectations about the effects of use.[60–62] These are all risk factors for illicit drug use more generally. We identified 3 factors for which empirical evidence indicates specificity in association with nonmedical prescription opioid use versus other illicit drugs.

Increased Availability and Access

Prescription opioids became widely available in the mid-1990s. Between 1997 and 2007, per capita retail purchases of methadone, hydrocodone, and oxycodone increased 13-fold, 4-fold, and 9-fold, respectively.[63] By 2010, enough prescription opioids were sold to medicate every adult in the United States with a dose of 5 milligrams of hydrocodone every 4 hours for 1 month.[64]

A study of national trends found that during 1999 through 2008, overdose death rates, sales, and substance abuse treatment admissions related to prescription opioids increased in parallel.[64] This coincided with a larger movement in the medical community in the late 1990s to identify and treat pain as a fifth vital sign; bodies such as the American Pain Society established guidelines that included aggressive treatment of reported pain, and a campaign initiated by the Department of Veterans Affairs in part fueled the movement with the intention of improving pain management and treating chronic pain.[65–67]

Increased medical use of prescription opioids has resulted in increased access to opioids for nonmedical use, either through the nonmedical use of legitimately acquired prescriptions or through formal or informal distribution networks.[68–73] Studies indicate that the large majority of adults who use opioids nonmedically obtain them from friends and relatives or from street-level dealers.[68–73] A substantial proportion of overdose deaths and emergency department visits occurs among individuals who have never received a prescription.[10,74–76] The proliferation of illicit high-volume prescribers and clinics (so-called pill mills) has also contributed to increases in overdoses in states such as Florida and Texas.[18,77]

Although availability of and access to prescription opioids have clearly increased across all areas of the United States, evidence regarding changes in the availability and access of illicit drugs, such as heroin and cocaine, is more mixed. Data on emergency department visits suggest that emergency department visits for prescription opioids more than doubled from 2004 to 2010, whereas cocaine-related visits increased 10% and heroin-related visits decreased.[78] National survey research indicates no evidence of an increase in the proportion of adolescents and adults who report that drugs such as marijuana are fairly easy or very easy to obtain over the past 10 years[79] (we did not assess comparable data on opioids), suggesting that the availability of nonopioid illicit drugs may not be keeping pace with the availability of prescription opioids, at least among adolescents.

However, data from the National Drug Threat Assessment indicates that heroin and cocaine availability is increasing nationally,[80] although information on comparisons with availability of prescription opioids is not available. Although the available evidence thus suggests that increases in prescription opioid availability have outpaced that of illicit drugs, the nonmedical prescription opioid use epidemic may portend future increases in illicit drug use as well, considering that nonmedical prescription opioid users are more likely than are nonusers to transition to heroin and other illicit drugs.[81]

Lower Perceptions of Harm

Adolescents perceive prescription opioids such as OxyContin and Vicodin as more harmful than other prescription drugs such as Adderall and amphetamines, but they perceive prescription opioid use as less harmful than the use of almost all other drugs except

experimental alcohol and occasional marijuana use.[82] Lower perceptions of harm for prescription opioids compared with other illicit drugs could be owing to 2 factors.

First, opioid use for pain management is increasingly common; thus, nonmedical users observe and are acquainted with the effective pharmacological action of the drugs among individuals in social and kin networks. Second, prescription opioid use does not necessarily involve routes of transmission with higher social stigma and greater adverse health consequences such as smoking, snorting, and injecting,[83,84] although some evidence indicates that rural nonmedical prescription opioid users are more likely to use nonoral modes of administration than are urban users.[85,86]

Self-Medicating for Pain

When used as prescribed under medical supervision, opioid analgesics are effective and used as standard practice in managing acute and chronic pain.[87,88]

Because of the fast action in reducing pain and anxiety symptoms, many individuals who overuse legitimate prescriptions or obtain prescription opioids illegally do so to manage existing chronic or acute pain or emotional problems.[89]

RURAL AREA USE VS URBAN AREA USE

We next considered specific factors that might explain the urban versus rural differences in nonmedical prescription opioid use. We hypothesized that 4 factors might be particularly relevant in explaining these patterns. These hypotheses have an empirical basis but require testing.

More Increased Availability in Rural Than Urban Areas

Although availability of prescription opioids has increased in all areas, there is evidence that it has increased more in rural areas. Specifically, per capita sales data indicate that states with large rural populations such as West Virginia are among the highest prescribers of opioid analgesics. The data are not entirely consistent with increased availability in rural areas, however, with Florida being a central outlier.

Several nonrural counties in Florida have the highest mean milligrams of opioids dispensed as of 2008,[90] and many of the top-prescribing doctors and clinics are in the state of Florida, although recent data indicate that control measures are reducing diversion of and doctor shopping for opioids in Florida.[91] Considering the evidence in total, however, a general picture emerges whereby high prescription rates in many rural counties indicate increased availability in these areas. The marketing of prescription opioids such as OxyContin has been more aggressive in rural communities such as those surrounding Appalachia.[92]

Rural populations are on average older than are urban populations[93,94]; thus, there may be more chronic pain for which management with opioid analgesics is indicated. Furthermore, evidence indicates that chronic pain and injury are more common in rural than in urban areas.[95–97] Finally, qualitative research indicates that prescription drug use in rural areas such as Appalachian Kentucky is an embedded part of the culture of the area, with prescription narcotics often prescribed to maintain a steady workflow in mines and other heavy labor occupations.[98] A higher density of available opioids may create opportunities for illegal markets in rural areas because family and friends are a primary distribution source of nonmedical prescription opioids.[68–73,99]

Out-Migration of Young People

In the past 2 decades, rural areas have evidenced an out-migration of many young adults during peak producing ages. For example, data from the 2010 census indicated that the percentage of individuals older than 65 years in West Virginia (which has a high proportion of rural counties) is twice the percentage of those aged 18 to 24 years (in 1970 the percentages of these 2 age groups were approximately equal).[100]

There are 2 consequences of this out-migration that may be related to increases in nonmedical prescription opioid use in rural areas. First is the effect on the economic conditions of the area. Areas with an aging workforce have less new economic infrastructure.[93,101,102] Adverse economic conditions and high rates of unemployment may create greater vulnerability to drug use in these populations. Second is a selection effect. Young adults who stay in economically deprived areas may have a greater accumulation of risk factors for problematic drug use and may be more likely to have established drug dependencies at a young age that cause downward social drift.

Although data on young adult migration patterns in the United States are scant, substantial research has documented that adolescents in rural areas overall have lower academic aspirations and academic achievement[103,104] as well as fewer returns on academic investment.[103–105] Individuals who have the material resources and aspirations to migrate to urban areas are likely different from individuals who stay on an array of risk factors for drug use, including educational attainment. Data on differences in young adult migration as it relates to risk factors for prescription opioid use are critical for testing and advancing these hypotheses.

Social and Kinship Networks

The influence of family structures and family life is a central cultural difference between rural life and urban life. Although rural areas are increasingly connected to urban spaces as urbanization continues in the United States, there are substantial differences in social norms, expectations, and cultural values between families of rural versus urban areas.[106–108] For example, in many rural areas a higher value is placed on work and on investment in the community than on education.[109] Individuals in rural areas report knowing the members of their social network longer and being more closely related to members of their social network than are individuals in urban areas.[106] Furthermore, substantial sociological research has documented that individuals in rural areas trust their neighbors more and are more likely to engage socially with neighbors and others who are geographically close.[108,110] Ties to the community are often stronger in rural areas, and greater value is placed on maintaining strong social capital.[107]

In the context of such strong social and kinship networks, economic hardship associated with industrial restructuring and rural to urban migration of youths may generate

strain not only in affected individuals but also in the broader social network, increasing the risk for illicit drug use across the social structure.[107] However, strong social ties with family and community may serve as a buffer against the stress of economic hardship,[111] in which case strong social ties would be associated with reduced drug use in rural areas. Testing and differentiating these pathways are critical for advancing our understanding of rural communities and drug use.

Family structures in rural areas are also larger and fertility rates are higher,[112] suggesting that rural kinship networks are often wider than are urban kinship networks. Substantial empirical evidence indicates that, in contrast to the sources of other illicit drugs, one of the main sources of illicit prescription opioids is the diversion of prescriptions legitimately filled by parents, relatives, friends, or acquaintances.[68–72,99] Thus, family networks matter more for prescription drugs than for other drugs because they are more often obtained from family members, whereas other drugs are more often obtained through friends or the drug trade.

Interestingly, OxyContin use has been significantly associated with increased social capital in rural areas,[113] suggesting that nonmedical prescription opioid distribution networks integrate into social networks in important ways in isolated rural communities. The breadth and proximity of the social network in rural areas may allow faster diffusion of prescription drugs to potential nonmedical users, and sources of prescription opioids through families may be more accessible in rural areas. These wide social networks with close ties across individuals may facilitate the distribution of prescription opioid medication. Little research has mapped social networks of prescription opioid diversion in rural areas; the hypotheses we have outlined provide a road map for addressing the potential differences in diversion and dissemination of prescription opioids in rural versus urban settings.

Structural Stressors of Modern Rural Living

Although there are stressors associated with living in both urban and rural areas, economic downturns have more adversely affected rural areas in the United States[114]; thus, stress owing to unemployment and lack of available industry may be more strongly felt in rural areas. It has been well documented that geographical context shapes risk of drug use,[21,22,25,115–117] including poverty and unemployment.[27,28,118–124] Rural counties in particular have faced job sector and industry shifts as populations shift to meet the labor demands of changing markets,[125,126] resulting in long-term economic deprivation, high rates of unemployment, and fewer opportunities for establishing a long-term career with potential for upward mobility.[125]

Numerous economic analyses have revealed mismatches between the skills of residents and the jobs available to them, and industrial restructuring predicts a shift into poverty of many in the United States.[24,80] Furthermore, in the United States, there have been decreases in the wage rate for low-skilled jobs[126] and the demand for manufacturing jobs[127] coupled with an increase in the demand for high-skilled workers.[80,86] These factors affect rural more than urban counties,[127] which generally have a greater diversity of labor markets and workers.

SUMMARY AND FUTURE DIRECTIONS

In the box on this page we have summarized our hypotheses regarding the responsible drivers of the increased prescription opioid misuse in rural areas. We posited that increases could, in part, be attributed to (1) increased sales of opioid analgesics in rural areas that lead to greater availability for nonmedical use through drug diversion networks, (2) out-migration of upwardly mobile young adults from rural areas that increases economic deprivation and creates an aggregation of young adults at high risk for drug use, (3) tight kinship and social networks that allow faster diffusion of nonmedical prescription opioids among those at risk, and (4) increasing economic deprivation and unemployment that create a stressful environment that places individuals at risk for drug use. These factors interact in dynamic ways with identified risk factors that are not unique to nonmedical prescription opioid use to lead to epidemics of prescription opioid use and associated injury in rural areas.

The hypotheses we have proposed do not explain all the observed patterns of nonmedical prescription opioid use and overdose. For example, states such as Florida and Washington have relatively high rates of nonmedical prescription opioid overdose but are largely urban, whereas Iowa and North Dakota have relatively low rates despite substantial rural areas[11,18,128]; thus, the mapping of rural geographical area to increases in nonmedical prescription opioid overdose is not linear.

Furthermore, demographic factors in both urban and rural areas likely interact with the factors we have mentioned in ways that remain to be elaborated. For example, Black and Hispanic individuals face the same if not greater stress because of economic hardship than do Whites and yet have lower overall rates of nonmedical prescription opioid use.[52,53] The intersection of demographic factors such as race and ethnicity with drug and alcohol use remains among the unexplained anomalies in the epidemiological literature on substance use.[129]

Finally, although we focused on prescription opioids, there is growing evidence that the abuse of other prescription drugs such as stimulants and benzodiazepines is also

Four Factors That Explain Increases in Nonmedical Prescription Opioid Misuse in Rural More Than Urban Areas

1. Increased sales of opioid analgesics in rural areas lead to greater availability for nonmedical use through diversion.
2. Out-migration of upwardly mobile young adults from rural areas increases economic deprivation and creates an aggregation of young adults at high risk for drug use.
3. Tight kinship and social networks allow faster diffusion of nonmedical prescription opioids among those at risk.
4. Increasing economic deprivation and unemployment create a stressful environment that places individuals at risk.

increasing,[57,125] especially among adolescents and young adults.[82] Understanding the distinctions among underlying risk factors for misuse of distinct types of prescription drugs is an important public health priority, as prevention and intervention strategies may differ depending on the type of drug.

The differences in drug use between urban and rural areas are just 1 example of how macrolevel forces shape population-level patterns of drug use. A comprehensive understanding of why, for example, rates of alcohol and drug use differ across time, across countries, in countries across states, and across certain population subgroups is critical and understudied. Social norms, cultural traditions, attitudes, availability, and policies are all likely critical to understanding broad differences in prevalence of substance use across areas,[21,36,51,130] yet few efforts have been made to comprehensively collect this information across time and across geographical spaces to examine the influence and the interaction of these factors with more microlevel determinants such as families, peers, and genetics.

We suggest that a strategic comparison between groups with different outcomes is an important way forward for the study of macrolevel influences on substance use. We have demonstrated that comparing urban and rural drug use is one way to find variation in structural factors that affect individual-level risk, yet empirical data to test our model remain critical.

National studies with sufficient sample sizes of urban and rural adolescents, young adults, and older adults with information on the economic and social characteristics of geographical spaces such as counties and neighborhoods are needed to advance this literature. Furthermore, the incorporation of novel methods such as agent-based or other generative modeling[12,124] would be useful to correctly develop empirical tests in the context of a dynamic social and political space where individuals interact in networks and with their surroundings.

The crisis of nonmedical use of prescription opioids is an important public health priority, and the greatest public health threat remains concentrated in rural, low-income areas of the United States. Responding to this threat requires new theories from which new hypotheses can be developed and new data and methods that can be used to test novel hypotheses. Increased understanding of spatial factors is critical for developing a better model for the etiology of substance use considering the importance of physical setting, as well as for identifying points of intervention and prevention at a population level. ■

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No protocol approval was necessary because no human participants were involved in this study.

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COMPLAINT

EXHIBIT #16

Obama 9499

September 16, 2016

Pres. Proc. No. 9499, 81 FR 65173, 2016 WL 5118847(Pres.)
Proclamation 9499

Prescription Opioid and Heroin Epidemic Awareness Week, 2016

September 16, 2016

***65173 By the President of the United States of America**

A Proclamation

Each year, more Americans die from drug overdoses than in traffic accidents, and more than three out of five of these deaths involve an opioid. Since 1999, the number of overdose deaths involving opioids, including prescription opioid pain relievers, heroin, and fentanyl, has nearly quadrupled. Many people who die from an overdose struggle with an opioid use disorder or other substance use disorder, and unfortunately misconceptions surrounding these disorders have contributed to harmful stigmas that prevent individuals from seeking evidence-based treatment. During Prescription Opioid and Heroin Epidemic Awareness Week, we pause to remember all those we have lost to opioid use disorder, we stand with the courageous individuals in recovery, and we recognize the importance of raising awareness of this epidemic.

Opioid use disorder, or addiction to prescription opioids or heroin, is a disease that touches too many of our communities_big and small, urban and rural_and devastates families, all while straining the capacity of law enforcement and the health care system. States and localities across our country, in collaboration with Federal and national partners, are working together to address this issue through innovative partnerships between public safety and public health professionals. The Federal Government is bolstering efforts to expand treatment and opioid abuse prevention activities, and we are working alongside law enforcement to help get more people into treatment instead of jail.

My Administration is steadfast in its commitment to reduce overdose deaths and get more Americans the help they need. That is why I continue to call on the Congress to provide $1.1 billion to expand access to treatment services for opioid use disorder. These new investments would build on the steps we have already taken to expand overdose prevention strategies, and increase access to naloxone_the overdose reversal drug that first responders and community members are using to save lives. We are also working to improve opioid prescribing practices and support targeted enforcement activities. Although Federal agencies will continue using all available tools to address opioid use disorder and overdose, the Congress must act quickly to help more individuals get the treatment they need_because the longer we go without congressional action on this funding, the more opportunities we miss to save lives.

Too often, we expect people struggling with substance use disorders to self-diagnose and seek treatment. And although we have made great strides in helping more Americans access care, far too many still lack appropriate, evidence-based treatment. This week, we reaffirm our commitment to raising awareness about this disease and supporting prevention and treatment programs. Let us ensure everyone with an opioid use disorder can embark on the road to recovery, and together, let us begin to turn the tide of this epidemic.

NOW, THEREFORE, I, BARACK OBAMA, President of the United States of America, by virtue of the authority vested in me by the Constitution ***65174** and the laws of the United States, do hereby proclaim September 18 through September 24, 2016, as Prescription Opioid and Heroin Epidemic Awareness Week. I call upon all Americans to observe this week with appropriate programs, ceremonies, and activities that raise awareness about the prescription opioid and heroin epidemic.

IN WITNESS WHEREOF, I have hereunto set my hand this sixteenth day of September, in the year of our Lord two thousand sixteen, and of the Independence of the United States of America the two hundred and forty-first.

BARACK OBAMA

Pres. Proc. No. 949981 FR 651732016 WL 5118847(Pres.)

End of Document

COMPLAINT

EXHIBIT #17

Rudd MMWR

December 30, 2016

Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015

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On December 16, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

The U.S. opioid epidemic is continuing, and drug overdose deaths nearly tripled during 1999–2014. Among 47,055 drug overdose deaths that occurred in 2014 in the United States, 28,647 (60.9%) involved an opioid (*1*). Illicit opioids are contributing to the increase in opioid overdose deaths (*2,3*). In an effort to target prevention strategies to address the rapidly changing epidemic, CDC examined overall drug overdose death rates during 2010–2015 and opioid overdose death rates during 2014–2015 by subcategories (natural/semisynthetic opioids, methadone, heroin, and synthetic opioids other than methadone).* Rates were stratified by demographics, region, and by 28 states with high quality reporting on death certificates of specific drugs involved in overdose deaths. During 2015, drug overdoses accounted for 52,404 U.S. deaths, including 33,091 (63.1%) that involved an opioid. There has been progress in preventing methadone deaths, and death rates declined by 9.1%. However, rates of deaths involving other opioids, specifically heroin and synthetic opioids other than methadone (likely driven primarily by illicitly manufactured fentanyl) (*2,3*), increased sharply overall and across many states. A multifaceted, collaborative public health and law enforcement approach is urgently needed. Response efforts include implementing the CDC *Guideline for Prescribing Opioids for Chronic Pain* (*4*), improving access to and use of prescription drug monitoring programs, enhancing naloxone distribution and other harm reduction approaches, increasing opioid use disorder treatment capacity, improving linkage into treatment, and supporting law enforcement strategies to reduce the illicit opioid supply.

The National Vital Statistics System multiple cause-of-death mortality files were used to record drug overdose deaths.† Drug overdose deaths were identified using the *International Classification of Disease, Tenth Revision* (ICD-10), based on the ICD-10 underlying cause-of-death codes X40–44 (unintentional), X60–64 (suicide), X85 (homicide), or Y10–Y14 (undetermined intent). Among deaths with drug overdose as the underlying cause, the type of opioid is indicated by the following ICD-10 multiple cause-of-death codes: opioids (T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6); natural/semisynthetic opioids (T40.2); methadone (T40.3); synthetic opioids other than methadone (T40.4); and heroin (T40.1). Some deaths involved more than one type of opioid; these deaths were included in the rates for each subcategory. Therefore, categories of deaths presented are not mutually exclusive.§

Changes in drug overdose death rates were analyzed for all 50 states and the District of Columbia (DC) from 2010 to 2015 using joinpoint regression.¶ Opioid overdose death rates were examined for the period 2014–2015 by subcategories (natural/semisynthetic opioids, methadone, heroin, and synthetic opioids other than methadone) and by demographics, region, and across states. State-level analyses were conducted for 28 states meeting the following criteria: 1) >80% of drug overdose death certificates named at least one specific drug in 2014; 2) change from 2014 to 2015 in the percentage of death certificates reporting at least one specific drug was <10 percentage points**; and 3) ≥20 deaths occurred during 2014 and 2015 in at least two opioid subcategories examined. Analyses comparing changes in age-adjusted death rates from 2014 to 2015 used z-tests when deaths were ≥100 and nonoverlapping confidence intervals based on a gamma distribution when deaths were <100.††

The drug overdose death rate increased significantly from 12.3 per 100,000 population in 2010 to 16.3 in 2015. Death rates increased in 30 states and DC and remained stable in 19 states (Figure). Two states had changing trends during this period of decreasing rates followed by increases.§§ During 2015, a total of 52,404 persons in the United States died from

* Natural opioids include morphine and codeine, and semisynthetic opioids include drugs such as oxycodone, hydrocodone, hydromorphone, and oxymorphone. Methadone is a synthetic opioid. Synthetic opioids, other than methadone, include drugs such as tramadol and fentanyl. Heroin is an illicit opioid synthesized from morphine that can be a white or brown powder, or a black sticky substance.

† https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm.

§ For example, a death involving both a synthetic opioid other than methadone and heroin would be included in both the "synthetic other than methadone" and heroin death rates.

¶ For all analyses, a p-value of <0.05 was considered to be statistically significant. https://surveillance.cancer.gov/joinpoint/.

** States whose reporting of any specific drug or drugs involved in an overdose changed by ≥10 percentage points from 2014 to 2015 were excluded, because drug-specific overdose numbers and rates might change substantially from 2014 to 2015 because of changes in reporting.

†† Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S. Census standard population age distribution https://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf. For z-tests, a p-value of <0.05 was considered to be statistically significant.

§§ Florida and South Carolina, had both decreasing and increasing trends during this period. In Florida, rates decreased from 2010 to 2013, then increased to 2015; in South Carolina, rates decreased from 2010 to 2012, then increased to 2015.

Summary

What is already known about this topic?

The U.S. opioid epidemic is continuing. Drug overdose deaths nearly tripled during 1999–2014. In 2014, among 47,055 drug overdose deaths, 61% involved an opioid. During 2013–2014, deaths associated with the most commonly prescribed opioids (natural/semisynthetic opioids) continued to increase slightly; however, the rapid increase in deaths appears to be driven by heroin and synthetic opioids other than methadone.

What is added by this report?

From 2014 to 2015, the death rate from synthetic opioids other than methadone, which includes fentanyl, increased by 72.2%, and heroin death rates increased by 20.6%. Rates of death involving heroin and synthetic opioids other than methadone increased across all demographic groups, regions, and in numerous states. Natural/semisynthetic opioid death rates increased by 2.6%, whereas, methadone death rates decreased by 9.1%.

What are the implications for public health practice?

There is an urgent need for a multifaceted, collaborative public health and law enforcement approach to the opioid epidemic, including implementing the CDC *Guideline for Prescribing Opioids for Chronic Pain*; improving access to and use of prescription drug monitoring programs; expanding naloxone distribution; enhancing opioid use disorder treatment capacity and linkage into treatment, including medication-assisted treatment; implementing harm reduction approaches, such as syringe services program; and supporting law enforcement strategies to reduce the illicit opioid supply.

a drug overdose, an increase from 47,055 in 2014; among these deaths, 33,091 (63.1%) involved an opioid, an increase from 28,647 in 2014. The age-adjusted opioid-involved death rate increased by 15.6%, from 9.0 per 100,000 in 2014 to 10.4 in 2015, driven largely by increases in deaths involving heroin and synthetic opioids other than methadone. Death rates for natural/semisynthetic opioids, heroin, and synthetic opioids other than methadone increased by 2.6%, 20.6%, and 72.2%, respectively (Table 1) (Table 2). Methadone death rates decreased by 9.1% (Table 1).

During 2014–2015, rates of natural/semisynthetic opioid deaths increased among males overall, both sexes aged 25–44 years, and non-Hispanic whites. Methadone death rates decreased among males and females overall, but increased among persons aged ≥65 years (Table 1). Death rates involving heroin and synthetic opioids other than methadone increased in both males and females, persons aged ≥15 years, and all racial/ethnic populations; however, heroin death rates among males aged 15–24 years remained stable. In 2015, death rates involving synthetic opioids other than methadone were highest among males aged 25–44 years (8.9 per 100,000), increasing 102.3% from 2014 to 2015 (Table 2). Heroin death rates also were highest in this demographic group (13.2), increasing 22.2% from 2014 to 2015. Natural/semisynthetic opioid death rates increased in the Northeast and South U.S. Census regions, and methadone death rates decreased in the South (Table 1). Death rates involving synthetic opioids other than methadone and heroin increased in all regions from 2014 to 2015 (Table 2).

Among the 28 states meeting inclusion criteria for state-level analyses, 16 (57.1%) experienced increases in death rates involving synthetic opioids other than methadone, and 11 (39.3%) experienced increases in heroin death rates from 2014 to 2015. The largest absolute rate change in deaths from synthetic opioids other than methadone occurred in Massachusetts, New Hampshire, Ohio, Rhode Island and West Virginia. The largest percentage increases in rates occurred in New York (135.7%), Connecticut (125.9%) and Illinois (120%) (Table 2). Connecticut, Massachusetts, Ohio, and West Virginia experienced the largest absolute rate changes in heroin deaths, while the largest percentage increases in rates occurred in South Carolina (57.1%), North Carolina (46.4%), and Tennessee (43.5) (Table 2). Three states (New Mexico, Oklahoma, and Virginia) experienced decreases in natural/semi-synthetic opioid death rates, while increases occurred in five states (Massachusetts, New York, North Carolina, Ohio, and Tennessee) (Table 1).

Discussion

During 2010–2015, the rate of drug overdose deaths in the United States increased in 30 states and DC, remained stable in 19 states, and showed decreasing trends followed by increases in two states.[§§,¶¶] From 2014 to 2015, drug overdose deaths increased by 5,349 (11.4%), signifying a continuing trend observed since 1999 (*1*). Opioid death rates increased by 15.6% from 2014 to 2015. These significant increases in death rates were driven by synthetic opioids other than methadone (72.2%), most likely illicitly-manufactured fentanyl (*2,3*), and heroin (20.6%). Increases in these opioid subcategories occurred overall and across all demographics and regions. Natural/semisynthetic opioid death rates increased by 2.6%, whereas methadone death rates decreased by 9.1%.

These findings are consistent with recent reports highlighting the increasing trend in deaths involving heroin and synthetic opioids other than methadone (*1–3,5*). The number of deaths involving synthetic opioids other than methadone have been associated with the number of drug products obtained by law enforcement testing positive for fentanyl, but not with fentanyl prescribing rates (*2,3*). A recent report found that these increases, likely attributable to illicitly manufactured fentanyl, were concentrated in eight of 27 states examined (*2*).

¶¶ https://www.cdc.gov/drugoverdose/data/statedeaths.html.

FIGURE. Age-adjusted rate* of drug overdose deaths,† by state — 2010 and 2015§

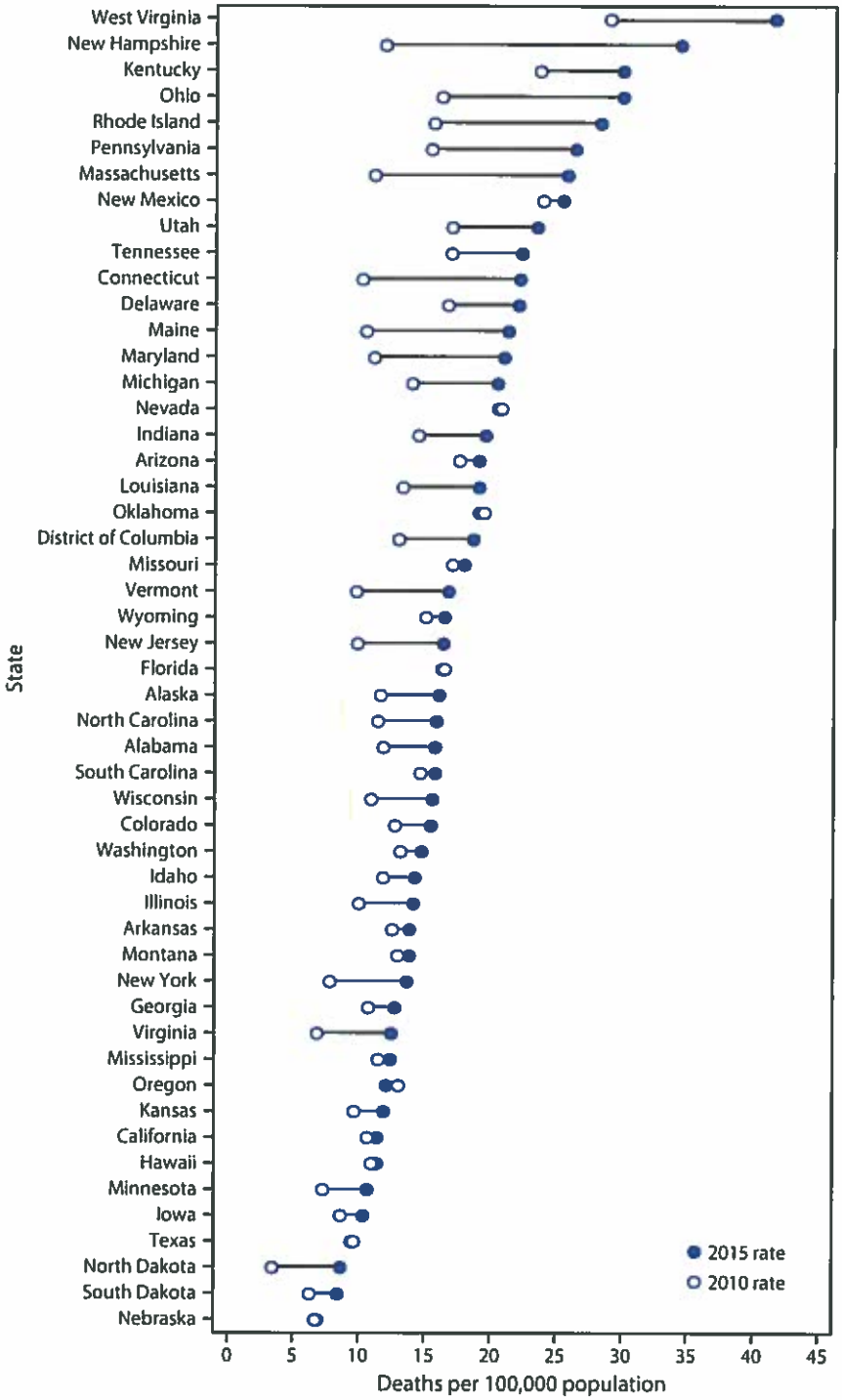

TABLE 1. Number and age-adjusted rate of drug overdose deaths* involving natural and semisynthetic opioids† and methadone,§,¶ by sex, age group, race/ethnicity, U.S. Census region, and selected states†† — United States, 2014 and 2015**

	Natural and semisynthetic opioids			Methadone		
	2014	2015	% change in rate,	2014	2015	% change in rate,
Characteristic	No. (Rate)	No. (Rate)	2014 to 2015	No. (Rate)	No. (Rate)	2014 to 2015
Overall	12,159 (3.8)	12,727 (3.9)	2.6§§	3,400 (1.1)	3,301 (1.0)	-9.1§§
Sex						
Male	6,732 (4.2)	7,117 (4.4)	4.8§§	2,009 (1.3)	1,939 (1.2)	-7.7§§
Female	5,427 (3.3)	5,610 (3.4)	3.0	1,391 (0.9)	1,362 (0.8)	-11.1§§
Age group (yrs)						
0–14	42 (0.1)	48 (0.1)	0.0	14 –¶¶	13 –¶¶	–¶¶
15–24	726 (1.7)	715 (1.6)	-5.9	241 (0.5)	201 (0.5)	0.0
25–34	2,115 (4.9)	2,327 (5.3)	8.2§§	796 (1.8)	735 (1.7)	-5.6
35–44	2,644 (6.5)	2,819 (6.9)	6.2§§	768 (1.9)	739 (1.8)	-5.3
45–54	3,488 (8.0)	3,479 (8.1)	1.3	854 (2.0)	843 (2.0)	0.0
55–64	2,437 (6.1)	2,602 (6.4)	4.9	629 (1.6)	642 (1.6)	0.0
≥65	706 (1.5)	736 (1.5)	0.0	98 (0.2)	127 (0.3)	50.0§§
Sex/Age group (yrs)						
Male						
15–24	529 (2.3)	493 (2.2)	-4.3	173 (0.8)	149 (0.7)	-12.5
25–44	2,869 (6.8)	3,139 (7.4)	8.8§§	969 (2.3)	926 (2.2)	-4.3
45–64	3,015 (7.4)	3,095 (7.5)	1.4	808 (2.0)	777 (1.9)	-5.0
Female						
15–24	197 (0.9)	222 (1.0)	11.1	68 (0.3)	52 (0.2)	-33.3
25–44	1,890 (4.5)	2,007 (4.8)	6.7§§	595 (1.4)	548 (1.3)	-7.1
45–64	2,910 (6.8)	2,986 (6.9)	1.5	675 (1.6)	708 (1.6)	0.0
Race/Ethnicity**						
White, non-Hispanic	10,308 (5.0)	10,774 (5.3)	6.0§§	2,845 (1.4)	2,725 (1.4)	0.0
Black, non-Hispanic	814 (2.0)	878 (2.1)	5.0	256 (0.6)	247 (0.6)	0.0
Hispanic	727 (1.4)	780 (1.5)	7.1	228 (0.5)	235 (0.5)	0.0
U.S. Census region of residence						
Northeast	1,851 (3.3)	2,095 (3.6)	9.1§§	587 (1.0)	643 (1.1)	10.0
Midwest	2,205 (3.3)	2,302 (3.4)	3.0	675 (1.0)	673 (1.0)	0.0
South	5,101 (4.2)	5,374 (4.4)	4.8§§	1,298 (1.1)	1,228 (1.0)	-9.1§§
West	3,002 (3.9)	2,956 (3.8)	-2.6	840 (1.1)	757 (1.0)	-9.1

See table footnotes on next page.

The decline in methadone death rates, a trend observed since 2008, followed efforts to reduce methadone use for pain, including Food and Drug Administration warnings, limits on high dose formulations, and clinical guidelines (*6*). The small increase in natural/semisynthetic opioid death rates illustrates an ongoing problem with prescription opioids; however, the increase has slowed from 2013–2014, potentially because of policy and health system changes, required prescription drug monitoring program review, legislative changes in naloxone distribution, and prescribing guidelines (*7*,*8*).***

The findings in this report are subject to at least five limitations. First, factors related to death investigation might affect rate estimates involving specific drugs. At autopsy, the substances tested for, and circumstances under which tests are performed to determine which drugs are present, might vary by jurisdiction and over time. Second, the percentage of deaths with specific drugs identified on the death certificate varies by jurisdiction and over time. Nationally, 19% (in 2014) and 17% (in 2015) of drug overdose death certificates did not include the specific types of drugs involved. Additionally, the percentage of drug overdose deaths with specific drugs identified on the death certificate varies widely by state, ranging from 47.4% to 99%. Variations in reporting across states prevent comparison of rates between states. Third, improvements in testing and reporting of specific drugs might have contributed to some observed increases in opioid-involved death rates. Fourth, because heroin and morphine are metabolized similarly (*9*), some heroin deaths might have been misclassified as morphine deaths, resulting in underreporting of heroin deaths. Finally,

*** Some state examples are available. New Mexico: https://nmhealth.org/news/information/2016/6/?view=429; https://nmhealth.org/news/information/2016/9/?view=484; and http://hscnews.unm.edu/news/education-program-successful-in-reducing-opioid-abuse010715; Oklahoma: https://www.ok.gov/health2/documents/UP_Oklahoma_Office_Based_Guidelines.pdf; Oregon: http://www.orpdmp.com. Washington: https://ajph.aphapublications.org/doi/abs/10.2105/AJPH.2014.302367?journalCode=ajph.

TABLE 1. (*Continued*) Number and age-adjusted rate of drug overdose deaths* involving natural and semisynthetic opioids† and methadone,§,¶ by sex, age group, race/ethnicity, U.S. Census region, and selected states†† — United States, 2014 and 2015**

Characteristic	Natural and semisynthetic opioids			Methadone		
	2014 No. (Rate)	2015 No. (Rate)	% change in rate, 2014 to 2015	2014 No. (Rate)	2015 No. (Rate)	% change in rate, 2014 to 2015
Selected states††						
States with very good or excellent reporting (n = 21)						
Alaska	40 (5.6)	51 (6.5)	16.1	12 –¶¶	10 –¶¶	–¶¶
Connecticut	157 (4.3)	183 (4.8)	11.6	50 (1.4)	72 (1.9)	35.7
Iowa	81 (2.7)	75 (2.5)	-7.4	16 –¶¶	24 (0.8)	–¶¶
Maine	80 (6.1)	102 (7.7)	26.2	29 (2.2)	36 (2.8)	27.3
Maryland	388 (6.2)	398 (6.5)	4.8	153 (2.4)	182 (2.9)	20.8
Massachusetts	178 (2.6)	225 (3.3)	26.9§§	88 (1.3)	82 (1.2)	-7.7
Nevada	224 (7.4)	259 (8.6)	16.2	64 (2.2)	57 (1.9)	-13.6
New Hampshire	81 (5.8)	63 (4.4)	-24.1	29 (2.3)	25 (1.9)	-17.4
New Mexico	223 (10.9)	160 (8.1)	-25.7§§	45 (2.3)	33 (1.6)	-30.4
New York	608 (3.0)	705 (3.4)	13.3§§	231 (1.1)	246 (1.2)	9.1
North Carolina	462 (4.7)	554 (5.5)	17.0§§	131 (1.4)	108 (1.1)	-21.4
Oklahoma	370 (9.6)	277 (7.2)	-25.0§§	67 (1.7)	62 (1.7)	0.0
Oregon	137 (3.2)	150 (3.6)	12.5	59 (1.4)	70 (1.7)	21.4
Rhode Island	70 (6.7)	95 (8.3)	23.9	24 (2.2)	30 (2.4)	9.1
South Carolina	319 (6.5)	322 (6.5)	0.0	77 (1.6)	57 (1.2)	-25.0
Utah	367 (13.6)	357 (12.7)	-6.6	47 (1.7)	45 (1.6)	-5.9
Vermont	21 (3.4)	25 (3.9)	14.7	–¶¶ –¶¶	–¶¶ –¶¶	–¶¶
Virginia	323 (3.9)	276 (3.3)	-15.4§§	105 (1.2)	67 (0.8)	-33.3§§
Washington	288 (3.8)	261 (3.5)	-7.9	115 (1.5)	111 (1.4)	-6.7
West Virginia	363 (20.2)	356 (19.8)	-2.0	35 (2.0)	29 (1.7)	-15.0
Wisconsin	279 (4.8)	249 (4.3)	-10.4	78 (1.4)	73 (1.3)	-7.1
States with good reporting (n = 7)						
Colorado	259 (4.6)	259 (4.5)	-2.2	51 (0.9)	34 (0.6)	-33.3
Georgia	388 (3.8)	435 (4.2)	10.5	124 (1.2)	115 (1.1)	-8.3
Illinois	253 (1.9)	271 (2.0)	5.3	106 (0.9)	99 (0.8)	-11.1
Minnesota	102 (1.9)	125 (2.2)	15.8	81 (1.6)	55 (1.0)	-37.5
Missouri	237 (4.0)	237 (3.9)	-2.5	53 (0.9)	62 (1.0)	11.1
Ohio	618 (5.4)	690 (6.1)	13.0§§	107 (0.9)	109 (1.0)	11.1
Tennessee	554 (8.6)	643 (9.7)	12.8§§	71 (1.1)	67 (1.0)	-9.1

Source: CDC. National Vital Statistics System, Mortality. CDC WONDER. Atlanta, GA: US Department of Health and Human Services, CDC; 2016. https://wonder.cdc.gov/.

* Rates are for the number of deaths per 100,000 population. Age-adjusted death rates were calculated using the direct method and the 2000 standard population. Deaths were classified using the *International Classification of Diseases, Tenth Revision* (ICD–10). Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

† Drug overdose deaths, as defined, that have natural and semisynthetic opioids (T40.2) as contributing causes.

§ Drug overdose deaths, as defined, that have methadone (T40.3) as a contributing cause.

¶ Categories of deaths are not exclusive because deaths might involve more than one drug. Summing categories will result in a number greater than the total number of deaths in a year.

** Data for Hispanic ethnicity should be interpreted with caution; studies comparing Hispanic ethnicity on death certificates and on census surveys have shown inconsistent reporting.

†† Analyses were limited to states meeting the following criteria. For states with very good to excellent reporting, ≥90% of drug overdose death certificates mention at least one specific drug in 2014, with the change in percentage of drug overdose deaths mentioning at least one specific drug differing by <10 percentage points from 2014 to 2015. States with good reporting had 80% to <90% of drug overdose death certificates mention at least one specific drug in 2014, with the change in the percentage of drug overdose deaths mentioning at least one specific drug differing by <10 percentage points from 2014 to 2015. Rate comparisons between states should not be made because of variations in reporting across states.

§§ Statistically significant at $p<0.05$ level. Gamma tests were used if the number of deaths was <100 in 2014 or 2015, and z-tests were used if the number of deaths was ≥100 in both 2014 and 2015.

¶¶ Cells with nine or fewer deaths are not reported, and rates based on <20 deaths are not considered reliable and not reported.

TABLE 2. Number and age-adjusted rate of drug overdose deaths* involving synthetic opioids other than methadone† and heroin,§,¶ by sex, age group, race/ethnicity, U.S. Census region, and selected states†† — United States, 2014 and 2015**

	Synthetic opioids other than methadone			Heroin		
Characteristic	2014 No. (Rate)	2015 No. (Rate)	% change in rate, 2014 to 2015	2014 No. (Rate)	2015 No. (Rate)	% change in rate, 2014 to 2015
Overall	5,544 (1.8)	9,580 (3.1)	72.2§§	10,574 (3.4)	12,989 (4.1)	20.6§§
Sex						
Male	3,465 (2.2)	6,560 (4.2)	90.9§§	8,160 (5.2)	9,881 (6.3)	21.2§§
Female	2,079 (1.3)	3,020 (1.9)	46.2§§	2,414 (1.6)	3,108 (2.0)	25.0§§
Age group (yrs)						
0–14	10 –¶¶	14 –¶¶	–¶¶	–¶¶ –¶¶	–¶¶ –¶¶	–¶¶
15–24	514 (1.2)	999 (2.3)	91.7§§	1452 (3.3)	1,649 (3.8)	15.2§§
25–34	1474 (3.4)	2,896 (6.6)	94.1§§	3493 (8.0)	4,292 (9.7)	21.3§§
35–44	1264 (3.1)	2,289 (5.6)	80.6§§	2398 (5.9)	3,012 (7.4)	25.4§§
45–54	1359 (3.1)	1,982 (4.6)	48.4§§	2030 (4.7)	2,439 (5.6)	19.1§§
55–64	742 (1.9)	1,167 (2.9)	52.6§§	1064 (2.7)	1,407 (3.4)	25.9§§
≥65	181 (0.4)	232 (0.5)	25.0§§	136 (0.3)	184 (0.4)	33.3§§
Sex/Age group (yrs)						
Male						
15–24	376 (1.7)	718 (3.2)	88.2§§	1,079 (4.8)	1,172 (5.2)	8.3
25–44	1,845 (4.4)	3,764 (8.9)	102.3§§	4,566 (10.8)	5,602 (13.2)	22.2§§
45–64	1,176 (2.9)	1,948 (4.7)	65.5§§	2,397 (5.9)	2,953 (7.2)	22.0§§
Female						
15–24	138 (0.6)	281 (1.3)	116.7§§	373 (1.7)	477 (2.2)	29.4§§
25–44	893 (2.1)	1,421 (3.4)	61.9§§	1,325 (3.2)	1,702 (4.0)	25.0§§
45–64	925 (2.2)	1,201 (2.8)	27.3§§	697 (1.6)	893 (2.1)	31.3§§
Race/Ethnicity**						
White, non-Hispanic	4,685 (2.4)	7,995 (4.2)	75.0§§	8,253 (4.4)	10,050 (5.4)	22.7§§
Black, non-Hispanic	449 (1.1)	883 (2.1)	90.9§§	1,044 (2.5)	1,310 (3.1)	24.0§§
Hispanic	302 (0.6)	524 (0.9)	50.0§§	1,049 (1.9)	1,299 (2.3)	21.1§§
U.S. Census region of residence						
Northeast	1,485 (2.7)	3,071 (5.6)	107.4§§	2,755 (5.1)	3,461 (6.3)	23.5§§
Midwest	1,319 (2.0)	2,548 (3.9)	95.0§§	3,385 (5.2)	3,959 (6.1)	17.3§§
South	2,087 (1.8)	3,303 (2.8)	55.6§§	2,733 (2.4)	3,722 (3.2)	33.3§§
West	653 (0.8)	658 (0.9)	12.5§§	1,701 (2.2)	1,847 (2.4)	9.1§§

See table footnotes on next page.

the state-specific analyses of opioid deaths are restricted to 28 states, limiting generalizability.

The ongoing epidemic of opioid deaths requires intense attention and action. In a November 2016 report, the Drug Enforcement Administration referred to prescription drugs, heroin, and fentanyl as the most significant drug-related threats to the United States.††† The misuse of prescription opioids is intertwined with that of illicit opioids; data have demonstrated that nonmedical use of prescription opioids is a significant risk factor for heroin use (*10*), underscoring the need for continued prevention efforts around prescription opioids. Intensifying efforts to distribute naloxone (an antidote to reverse an opioid overdose), enhancing access to treatment, including medication-assisted treatment, and implementing harm reduction services are urgently needed. It is important to focus efforts on expanding opioid disorder treatment capacity, including medication-assisted treatment and improving linkage into treatment.§§§ Implementing harm reduction approaches, such as the scaling up comprehensive syringe services programs can reach persons with opioid use disorders and provide them with access to naloxone and medication-assisted treatment, reduce transmission risk for human immunodeficiency virus or hepatitis C, and reduce other harms from drug use. Law enforcement strategies to reduce the illicit opioid supply must also be supported. A recent report did not find evidence that efforts to reduce opioid prescribing were leading to heroin overdoses; rather, such policies could help reduce the number of persons who are exposed to opioids (*7*). Continued improvements in guideline-recommended opioid prescribing practices for chronic pain (*4*), increased improving access to and use of prescription drug monitoring programs, and increased utilization of nonopioid pain treatments are needed. A multifaceted, coordinated approach between public health and public safety is also necessary to address the U.S. opioid epidemic.

††† https://www.dea.gov/resource-center/2016%20NDTA%20Summary.pdf.

§§§ http://aspe.hhs.gov/sites/default/files/pdf/107956/ib_OpioidInitiative.pdf.

TABLE 2. (*Continued*) Number and age-adjusted rate of drug overdose deaths* involving synthetic opioids other than methadone† and heroin,§,¶ by sex, age group, race/ethnicity, U.S. Census region, and selected states†† — United States, 2014 and 2015**

Characteristic	Synthetic opioids other than methadone			Heroin		
	2014 No. (Rate)	2015 No. (Rate)	% change in rate, 2014 to 2015	2014 No. (Rate)	2015 No. (Rate)	% change in rate, 2014 to 2015
Selected states††						
States with very good or excellent reporting (n = 21)						
Alaska	14 –¶¶	14 –¶¶	–¶¶	25 (3.3)	37 (4.7)	42.4
Connecticut	94 (2.7)	211 (6.1)	125.9§§	299 (8.9)	390 (11.3)	27.0§§
Iowa	29 (1.0)	44 (1.5)	50.0	37 (1.3)	45 (1.6)	23.1
Maine	62 (5.2)	116 (9.9)	90.4§§	38 (3.1)	52 (4.5)	45.2
Maryland	230 (3.8)	357 (5.8)	52.6§§	313 (5.2)	405 (6.6)	26.9§§
Massachusetts	453 (6.9)	949 (14.4)	108.7§§	469 (7.2)	634 (9.6)	33.3§§
Nevada	32 (1.0)	32 (1.1)	10.0	64 (2.2)	82 (2.7)	22.7
New Hampshire	151 (12.4)	285 (24.1)	94.4§§	98 (8.1)	78 (6.5)	-19.8
New Mexico	66 (3.3)	42 (2.1)	-36.4	139 (7.2)	156 (8.1)	12.5
New York	294 (1.4)	668 (3.3)	135.7§§	825 (4.2)	1,058 (5.4)	28.6§§
North Carolina	217 (2.2)	300 (3.1)	40.9§§	266 (2.8)	393 (4.1)	46.4§§
Oklahoma	73 (1.9)	93 (2.4)	26.3	26 (0.7)	36 (1.0)	42.9
Oregon	33 (0.8)	34 (0.9)	12.5	124 (3.2)	102 (2.5)	-21.9
Rhode Island	82 (7.9)	137 (13.2)	67.1§§	66 (6.8)	45 (4.3)	-36.8
South Carolina	110 (2.3)	161 (3.3)	43.5§§	64 (1.4)	100 (2.2)	57.1§§
Utah	68 (2.5)	62 (2.3)	-8.0	110 (3.8)	127 (4.3)	13.2
Vermont	21 (3.6)	33 (5.6)	55.6	33 (5.8)	33 (5.8)	0.0
Virginia	176 (2.1)	270 (3.3)	57.1§§	253 (3.1)	353 (4.3)	38.7§§
Washington	62 (0.8)	65 (0.9)	12.5	289 (4.1)	303 (4.2)	2.4
West Virginia	122 (7.2)	217 (12.7)	76.4§§	163 (9.8)	194 (11.8)	20.4
Wisconsin	90 (1.6)	112 (2.1)	31.3	270 (4.9)	287 (5.3)	8.2
States with good reporting (n = 7)						
Colorado	80 (1.5)	64 (1.2)	-20.0	156 (2.9)	159 (2.8)	-3.4
Georgia	174 (1.7)	284 (2.8)	64.7§§	153 (1.6)	222 (2.2)	37.5§§
Illinois	127 (1.0)	278 (2.2)	120.0§§	711 (5.6)	844 (6.7)	19.6§§
Minnesota	44 (0.8)	55 (1.0)	25.0	100 (1.9)	115 (2.2)	15.8
Missouri	109 (1.9)	183 (3.1)	63.2§§	334 (5.8)	303 (5.3)	-8.6
Ohio	590 (5.5)	1,234 (11.4)	107.3§§	1,208 (11.1)	1,444 (13.3)	19.8§§
Tennessee	132 (2.1)	251 (4.0)	90.5§§	148 (2.3)	205 (3.3)	43.5§§

Source: CDC. National Vital Statistics System, Mortality. CDC WONDER. Atlanta, GA: US Department of Health and Human Services, CDC; 2016. https://wonder.cdc.gov/.

* Rates are for the number of deaths per 100,000 population. Age-adjusted death rates were calculated using the direct method and the 2000 standard population. Deaths were classified using the *International Classification of Diseases, Tenth Revision* (ICD–10). Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

† Drug overdose deaths, as defined, that have synthetic opioids other than methadone (T40.4) as contributing causes.

§ Drug overdose deaths, as defined, that have heroin (T40.1) as a contributing cause.

¶ Categories of deaths are not exclusive because deaths might involve more than one drug. Summing categories will result in a number greater than the total number of deaths in a year.

** Data for Hispanic ethnicity should be interpreted with caution; studies comparing Hispanic ethnicity on death certificates and on census surveys have shown inconsistent reporting.

†† Analyses were limited to states meeting the following criteria. For states with very good to excellent reporting, ≥90% of drug overdose death certificates mention at least one specific drug in 2014, with the change in percentage of drug overdose deaths mentioning at least one specific drug differing by <10 percentage points from 2014 to 2015. States with good reporting had 80% to <90% of drug overdose death certificates mention at least one specific drug in 2014, with the change in the percentage of drug overdose deaths mentioning at least one specific drug differing by <10 percentage points from 2014 to 2015. Rate comparisons between states should not be made because of variations in reporting across states.

§§ Statistically significant at p<0.05 level. Gamma tests were used if the number of deaths was <100 in 2014 or 2015, and z-tests were used if the number of deaths was ≥100 in both 2014 and 2015.

¶¶ Cells with nine or fewer deaths are not reported, and rates based on <20 deaths are not considered reliable and not reported.

[1]Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC, [2]Epidemic Intelligence Service, CDC.

Corresponding authors: Rose A. Rudd, rvr2@cdc.gov, 770-488-3712; Puja Seth, pseth@cdc.gov, 404-639-6334.

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COMPLAINT

EXHIBIT #18

CDC Press Release

August 14, 2014

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Press Release 2014

For Immediate Release: Thursday, August 14, 2014
Contact: CDC Media Relations (http://www.cdc.gov/media)
(404) 639-3286

CDC awards over $1 Million to West Virginia to address prescription drug overdose prevention

Making a difference by serving as a model of prevention

The Centers for Disease Control and Prevention has announced that West Virginia will receive more than $1 million over the next three years to enhance its prescription drug monitoring program (PDMP).

The announcement was made last night by Daniel M. Sosin, M.D., M.P.H., F.A.C.P., acting director of CDC's National Center for Injury Prevention and Control at an event with U.S. Rep. Nick Rahall (WV-3). Officials from the White House Office of National Drug Control Policy, the Department of Justice's Office of Justice Programs and the Department of Health and Human Services' Substance Abuse and Mental Health Services Administration and National Institute of Drug Abuse, part of the National Institutes of Health, were also in attendance.

The funding will help the state to develop and implement a Medicaid Patient Review and Restriction Program and evaluate its innovative prescription drug overdose prevention policies.

"Prescription drug overdose is an epidemic in the United States. We remain committed to providing states with the resources, expertise, and data they need to protect patients and save lives," said CDC Director Tom Frieden, M.D., M.P.H. "States are at the front lines of this epidemic, and as the nation's public health agency CDC is committed to helping them any way we can."

West Virginia has the highest rate of drug overdose deaths in the United States.

- West Virginia had 36.3 drug overdose deaths per 100,000 people in 2011, nearly triple the U.S. rate (13.2/100,000). West Virginia also had 635 deaths from drug overdoses in 2011.
- Prescription drugs – opioids and benzodiazepines in particular – are major drivers of the drug overdose deaths in West Virginia.

Opioid prescribing rates in West Virginia is among the highest in the country.

- **IMS Health:** In 2012, West Virginia providers wrote 137.6 opioid pain reliever prescriptions per 100 people, the third highest prescribing rate in the country and far above the U.S. rate (82.5/100).

The Prescription Drug Overdose: Boost for State Prevention program will give states a surge of resources and direct support from CDC to advance the most promising prevention strategies. Overall, CDC has committed $6 million over the next three years to help five states (Kentucky, Oklahoma, Tennessee, Utah and West Virginia), improve their prescription drug monitoring programs, advance innovative public insurance programs to prevent opioid abuse, and conduct rigorous state policy evaluations to sharpen our understanding of the most effective prevention strategies. The advances made by these states could then serve as a model for the rest of the country.

CDC's Injury Center works to protect the safety of everyone, every day. For more information about prescription drug overdoses, please visit www.cdc.gov/drugoverdose/ (http://www.cdc.gov/drugoverdose/index.html).

U.S. Department of Health and Human Services (http://www.hhs.gov)

CDC works 24/7 (http://www.cdc.gov/24-7) saving lives and protecting people from health threats to have a more secure nation. Whether these threats are chronic or acute, manmade or natural, human error or deliberate attack, global or domestic, CDC is the U.S. health protection agency.

Page last reviewed: August 6, 2014
Page last updated: November 25, 2015
Content source: Content source: Centers for Disease Control and Prevention (/), National Center for Injury Prevention and Control

COMPLAINT

EXHIBIT #19

Attorney General Letters

AMA
AMERICAN MEDICAL ASSOCIATION

JAMES L. MADARA, MD
EXECUTIVE VICE PRESIDENT, CEO

ama-assn.org
t (312) 464-5000

August 2, 2016

The Honorable Patrick Morrisey
Attorney General
State of West Virginia
State Capitol Complex
Bldg. 1, Room E-26
Charleston, WV 25305

Dear Attorney General Morrisey:

On behalf of the physician and medical student members of the American Medical Association (AMA), I want to thank you for taking the time to meet with me while you were in Chicago and discuss ways to work more closely with the medical community. Based on the initiatives you discussed and your openness to consider new ideas, I am confident that there will be ample opportunities for us to work together. I look forward to continuing our conversation.

I first want to specifically commend your efforts to help reverse the opioid epidemic that has ravaged West Virginia. It is a tragic understatement to say that generations of families have been affected by opioid misuse, overdose and death. The AMA shares your belief that primary prevention and public education are key components of a public health plan to halt the epidemic and protect future generations.

To that end, I would like to offer a few comments on the "Suggested Best Practices for Prescribing Opioids in West Virginia" (Best Practices). I greatly appreciate your strong support for increasing access to naloxone and urging insurers to cover non-opioid and non-pharmacological treatments for pain. I would further encourage that affordable and accessible treatment for substance use disorders not be constrained by arbitrary limits by any public or private payer. This includes coverage for naloxone and medication assisted treatment (MAT) for opioid use disorders.

One final suggestion is to continue your work with the West Virginia State Medical Association, the state medical board and other stakeholders to further develop these Best Practices in such a way that with additional revisions, the Best Practices could be publicly supported and promoted by all stakeholders. With many different groups in West Virginia and elsewhere publishing their own "best practices," "recommendations," and "guidelines," we are concerned by the potential for mixed messages. It would be a great example for the country if all stakeholders in West Virginia could coalesce around a consistent standard that could be promoted throughout the state.

As I promised, I also wanted to provide a few thoughts about the National Governors Association (NGA) recent publications on best practices and policy recommendations on the opioid epidemic. The AMA has worked with the NGA for many years on this issue, and we are very proud of the fact that the NGA has adopted a public health focus – rather than one strictly based on law enforcement. The newest document,

"Finding Solutions to the Prescription Opioid and Heroin Crisis: A Road Map for States," contains many excellent policy options that have been debated – and enacted – across the country, including in West Virginia. The AMA supports many of those recommendations, and I would be happy to have my staff engage in a detailed discussion, but let me focus on one area that very few states have addressed.

As you know in West Virginia, there has been no shortage of legislative and regulatory action to affect prescribing behaviors as one strategy to reverse the epidemic. What is missing, however, is a thorough evaluation of these new policies – or existing laws that are designed to help provide treatment for substance use disorders. It is imperative that these laws be evaluated to determine if they are having their intended effect to improve patient care and reduce the harms from opioid misuse.

Finally, please know that the AMA would be happy to continue this discussion and others that affect patients. If there is an opportunity where you believe the AMA could contribute to a discussion among your fellow attorneys general on the opioid epidemic or other issues, please let us know. When those opportunities arise, please reach out directly to Daniel Blaney-Koen, JD, Senior Legislative Attorney, Advocacy Resource Center at daniel.blaney-koen@ama-assn.org or (312) 464-4954.

Thank you for your efforts in helping West Virginia's patients.

Sincerely,

James L. Madara, MD

cc: Brian O. Foy
Richard A. Deem

WEST VIRGINIA State Medical Association

August 9, 2016

Patrick Morrisey
Attorney General
State of West Virginia
Office of the Attorney General
State Capitol Building 1, Room 26-E
Charleston, WV 25305

Dear Attorney General Morrisey:

The West Virginia State Medical Association (WVSMA) is pleased to support your Best Practices initiatives.

We appreciated the opportunity to meet at your office with Anthony Martin, Chief Operating Officer and Senior Deputy Attorney General to discuss the initiatives, and to review the draft documents for Best Practices for Prescribing Opioids. It was a pleasure to speak with Mr. Martin and discuss our mutual interest in working toward an effective solution to the epidemic of opioid abuse that is plaguing our state.

Founded in 1867, the WVSMA is a physician-based organization which supports health care policies that promote the public health and encourages the highest quality continuing medical education. As physicians, our members are committed to providing the best possible care to their patients.

Your Best Practices for Prescribing Opioids promotes excellence in care, and, together with your guidelines for dispensers and health care payers, can provide an effective resource for health care professionals and others.

We are grateful for your efforts to work on this critical health care issue, and we look forward to continuing to work with you in the future.

Sincerely,

PJ Taylor MD

Paula Taylor, RPh, MD,
President

Brian Foy,
Executive Director

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KISHORE K. CHALLA, MD, FACC
VICE PRESIDENT

ROBERT C. KNITTLE
EXECUTIVE DIRECTOR

August 9, 2016

Office of the WV Attorney General
Attorney General Patrick Morrisey
State Capitol Complex
Building 1, Room E-26
Charleston, WV 25305

Attorney General Morrisey:

The West Virginia Board of Medicine congratulates you on your ongoing efforts to bring education and understanding to our citizens and medical professionals throughout the state regarding the improper prescribing and abuse of opioids drugs. For over a decade our state has been at the top if not led the nation in prescription drug overdose deaths. During this time period, over 5,000 of our friends, neighbors and colleagues have died as a result of the misuse and abuse of opioids. Thousands more have suffered and continue to deal with the effects of opioid addiction. Few, if any, have been unaffected in some way by this scourge.

For the past 16 years the Board of Medicine has squarely confronted this issue through the establishment and enforcement of regulation, policy, treatment and education of its almost 8,000 licensees. We welcome and support the recent Best Practice Plan campaign of the attorney general's office to increase the use of non-opioid alternatives as a first line treatment for acute and chronic pain thereby reducing the general use of opioids. Such best practices are in turn reflected in the 2016 Center for Disease Control Guideline for Prescribing Opioids for Chronic Pain as well as the mandated continuing medical education requirements for our licensees.

Only through such concerted and combined efforts will we begin to impact the opioid epidemic. We appreciate the opportunity to participate and support in your efforts.

Sincerely,

Robert C. Knittle

WV
Primary Care Association

August 9, 2016

Patrick Morrisey
Attorney General
State of West Virginia
Office of the Attorney General
State Capitol Building, Room 26-E
Charleston, West Virginia 25305

RE: Substance Abuse

Dear Attorney General Morrisey,

The West Virginia Primary Care Association (WVPCA) is pleased to support the Best Practices Initiatives developed by your office. West Virginia leads the nation in opioid deaths and has a drug addiction problem that is devastating families and communities across the state. The prescribing and dispensing documents promote best practices and lay the foundation for a more rigorous approach to resolving this crisis.

The WVPCA represents 31 community health centers across the state that provide high quality cost effective primary care to more than 411,000 West Virginians. Many of the health centers are providing integrated behavioral health services and seven health centers are now offering medication assisted treatment to patients requesting substance abuse assistance.

We are appreciative of your efforts to work collaboratively with providers across the state on this critical health issue and we look forward to working with again in the future.

Sincerely,

Louise Reese
CEO

1700 MacCorkle Avenue, SE – One South ♦ Charleston, WV 25314 ♦ 304.346.0032 ♦ Fax 304.346.0033 ♦
www.wvpca.org

COMPLAINT

EXHIBIT #20

Obama Memorandum

October 21, 2015

Administration of Barack Obama, 2015

Memorandum on Addressing Prescription Drug Abuse and Heroin Use
October 21, 2015

Memorandum for the Heads of Executive Departments and Agencies

Subject: Addressing Prescription Drug Abuse and Heroin Use

By the authority vested in me as President by the Constitution and the laws of the United States of America, and in order to reduce prescription pain medication and heroin overdose deaths, promote the appropriate and effective prescribing of pain medications, and improve access to treatment, I hereby direct the following:

Section 1. Policy. The epidemic of prescription pain medication and heroin deaths is devastating families and communities across the country. Prescription drugs—especially opioid pain medications—have been implicated increasingly in drug overdose deaths over the last decade. According to the Centers for Disease Control and Prevention (CDC), the number of overdose deaths involving prescription opioids quadrupled between 1999 and 2013, with more than 16,000 deaths in 2013. In recent years, overdose deaths involving heroin have sharply increased, nearly doubling between 2011 and 2013. The CDC has identified addiction to prescription pain medication as the strongest risk factor for heroin addiction.

One of the most significant ways to address these issues is to ensure that medical professionals receive adequate training on appropriate pain medication prescribing practices, and the risks associated with these medications. The Federal Government must do more to ensure that such training is provided on an ongoing basis to health care professionals prescribing pain medications. Work is already underway to achieve this goal across executive departments and agencies, but these efforts must be accelerated given the urgency of the problem. The training of Federal health care personnel in appropriate prescribing of controlled substances should be a model for similar initiatives developed across the country.

An additional priority in addressing prescription opioid pain medication misuse and heroin use is improved access to medication-assisted treatment (MAT). MAT is the use of Food and Drug Administration (FDA)-approved medications, such as buprenorphine, buprenorphine-naloxone combination products, methadone, and naltrexone—in combination with counseling, other behavioral therapies, and patient monitoring—to provide treatment for opioid use disorders. Only a small minority of Americans who might benefit from this treatment are receiving it. Federally administered health benefit programs can help to increase access to these services. These programs also can serve as models for reviewing and modernizing coverage policies and benefit management strategies in response to clinical prescribing guidelines and recommendations for the treatment of chronic pain. For example, a CDC study found that the use of methadone in pain treatment is associated with a disproportionately high number of overdose deaths compared to other opioid pain relievers. Federally administered health benefit programs can use benefit design and formulary management to take steps to reduce the risk of opioid use disorders.

Sec. 2. Training for Federal Prescribers. (a) Executive departments and agencies (agencies) shall, to the extent permitted by law, provide training on the appropriate and effective prescribing of opioid medications to all employees who are health care professionals and who prescribe controlled substances as part of their Federal responsibilities and duties.

Agencies also shall require all contractors who are health care professionals, spend 50 percent or more of their clinical time under contract with the Federal Government, and prescribe controlled substances under the terms and conditions of their contract or agreement with the Federal Government to obtain such training. These training requirements shall also be implemented for clinical residents and other clinical trainees who spend 50 percent or more of their clinical time practicing in an executive department or agency facility.

(b) The training must address, at a minimum, best practices for appropriate and effective prescribing of pain medications, principles of pain management, the misuse potential of controlled substances, identification of potential substance use disorders and referral to further evaluation and treatment, and proper methods for disposing of controlled substances. Training approaches may include both traditional continuing education models and models that pair intensive coaching for the highest volume prescribers with case-based courses for other prescribers. To the extent feasible, training adopted by agencies should be consistent with consensus guidelines on pain medication prescribing developed by the CDC.

(c) Agencies shall require all employees, contractors, and clinical residents and trainees described in subsection (a) of this section to complete training within 18 months of the date of this memorandum and a refresher course every 3 years thereafter.

Sec. 3. Improving Access to Medication-Assisted Treatment and Modernizing Benefit Design. (a) Agencies that directly provide health care services, contract to provide health care services, reimburse for health care services, or facilitate access to health benefits shall, to the extent available and permitted by law, review all health benefit requirements, drug formularies, program guidelines, medical management strategies, drug utilization review programs, and all other relevant policies, tools, and strategies in order to identify any barriers individuals with opioid use disorders would encounter in accessing MAT. This review also shall identify any current practices, such as use of methadone as a preferred or first-line pain management drug that are inconsistent with the goals of reducing opioid use disorders and overdoses.

(b) Not later than 90 days after the date of this memorandum, each agency described in subsection (a) of this section shall submit an action plan to the Directors of the White House Domestic Policy Council and the White House Office of National Drug Control Policy addressing the barriers and practices identified in their reviews.

(c) The Secretary of Health and Human Services shall make clinical and other experts from agencies within the Department of Health and Human Services, such as the National Institutes of Health, the CDC, the Substance Abuse and Mental Health Services Administration, and the FDA, available to consult with other agencies on their reviews as necessary.

Sec. 4. General Provisions. (a) Nothing in this memorandum shall be construed to impair or otherwise affect:

(i) the authority granted by law to a department or agency, or the head thereof; or

(ii) the functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.

(b) This memorandum shall be implemented consistent with applicable law and subject to the availability of appropriations.

(c) This memorandum is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity by any party against the United

States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.

BARACK OBAMA

Categories: Communications to Federal Agencies : Prescription drug abuse and heroin use, reduction efforts, memorandum.

Subjects: Drug abuse and trafficking : Addiction treatment and reduction efforts; Drug abuse and trafficking : Medication-assisted treatment, improvement efforts; Health and Human Services, Department of: Centers for Disease Control and Prevention; Health and medical care : Prescription narcotic access and availability, training for health care professionals.

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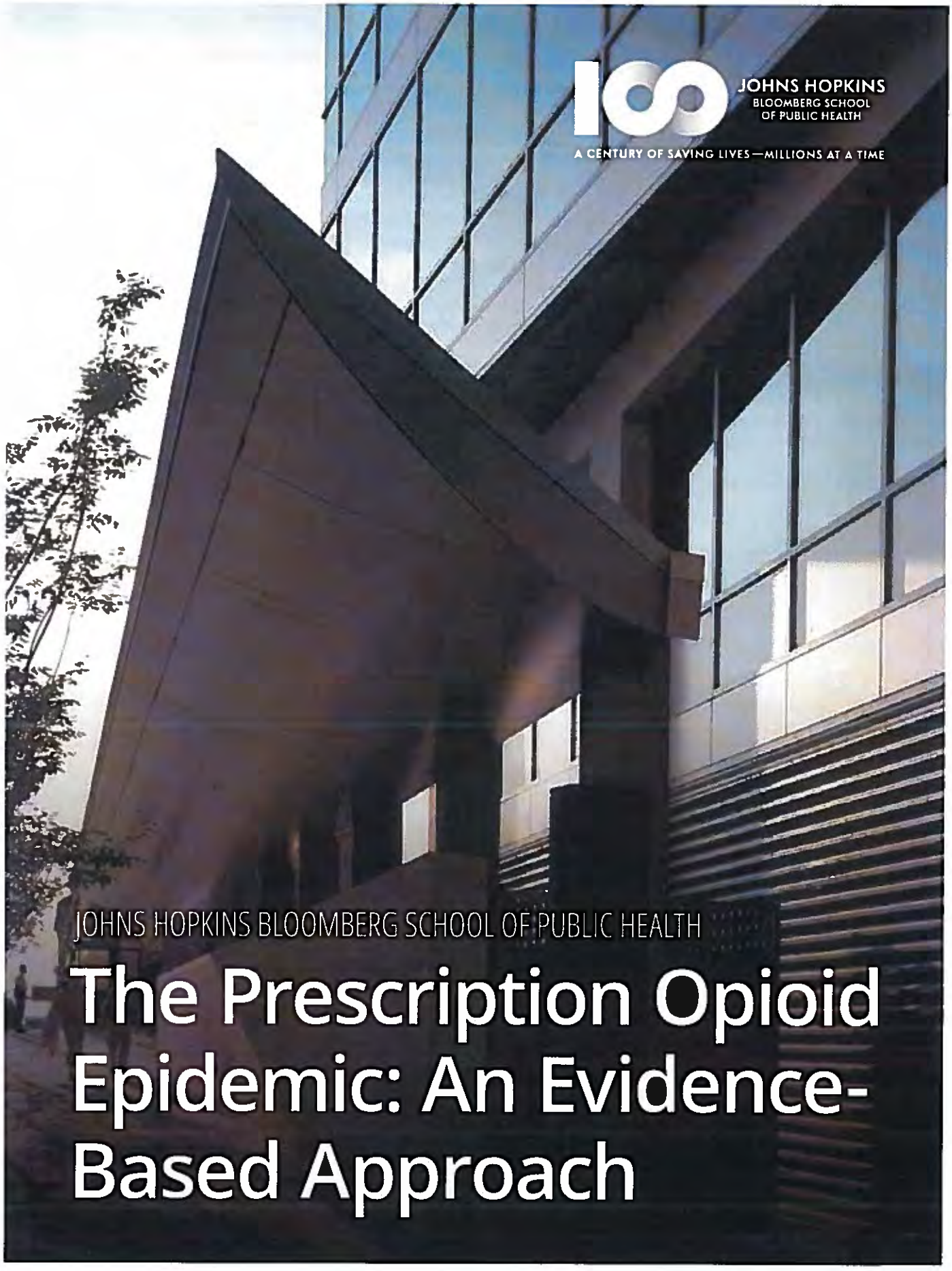
COMPLAINT

EXHIBIT #21

John Hopkins Report

November 2015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A CENTURY OF SAVING LIVES—MILLIONS AT A TIME
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The Prescription Opioid Epidemic: An Evidence-Based Approach

THE PRESCRIPTION OPIOID EPIDEMIC: AN EVIDENCE-BASED APPROACH

November 2015

PREPARED BY

Johns Hopkins Bloomberg School of Public Health,
Johns Hopkins Center for Drug Safety and Effectiveness,
and Johns Hopkins Center for Injury Research and Policy

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Executive Summary

Prescription drugs are essential to improving the quality of life for millions of Americans living with acute or chronic pain. However, misuse, abuse, addiction, and overdose of these products, especially opioids, have become serious public health problems in the United States. A comprehensive response to this crisis must focus on preventing new cases of opioid addiction, identifying early opioid-addicted individuals, and ensuring access to effective opioid addiction treatment while safely meeting the needs of patients experiencing pain.

At the invitation of the Johns Hopkins Bloomberg School of Public Health and the Clinton Foundation, a diverse group of experts were convened to chart a path forward to address these issues. After a town hall meeting at the School, featuring an inspiring call to action from President Bill Clinton[1], the group — including clinicians, researchers, government officials, injury prevention professionals, law enforcement leaders, pharmaceutical manufacturers and distributers, lawyers, health insurers and patient representatives — spent the next day and a half:

— Reviewing what is known about prescription opioid misuse, abuse, addiction and overdose;

— Identifying strategies for reversing the alarming trends in injuries, addiction, and deaths from these drugs; and

— Making recommendations for action.

Following this meeting, the group released a consensus statement with three guiding principles for translating the meeting discussion into actionable recommendations.[2]

INFORMING ACTION WITH EVIDENCE.

Some evidence-based interventions exist to inform action to address this public health emergency; these should be scaled up and widely disseminated. Furthermore, many promising ideas are evidence-informed, but have not yet been rigorously evaluated. The urgent need for action requires that we rapidly implement and carefully evaluate these promising policies and programs. The search for new, innovative solutions also needs to be supported.

INTERVENING COMPREHENSIVELY.

We support approaches that intervene all along the supply chain, and in the clinic, community and addiction treatment settings. Interventions aimed at stopping individuals from progressing down a pathway that will lead to misuse, abuse, addiction and overdose are needed. Effective primary, secondary and tertiary prevention strategies are vital. The importance of creating synergies across different interventions to maximize available resources is also critical.

PROMOTING APPROPRIATE AND SAFE USE OF PRESCRIPTION OPIOIDS.

Used appropriately, prescription opioids can provide relief to patients. However, these therapies are often being prescribed in quantities and for conditions that are excessive, and in many cases, beyond the evidence base. Such practices, and the lack of attention to safe use, storage and disposal of these drugs, contribute to the misuse, abuse, addiction and overdose increases that have occurred over the past decade. We support efforts to maximize the favorable risk/benefit balance of prescription opioids by optimizing their use in circumstances supported by best clinical practice guidelines.

Meeting participants formed seven working groups to make recommendations on: 1) prescribing guidelines, 2) prescription drug monitoring programs, 3) pharmacy benefit managers and pharmacies, 4) engineering strategies, 5) overdose education and naloxone distribution programs, 6) addiction treatment, and 7) community-based prevention.

1. www.jhsph.edu/rxtownhall2014
2. www.jhsph.edu/2014consensusstatement

Recommendations for Action

#1 PRESCRIBING GUIDELINES

1.1 Repeal existing permissive and lax prescription laws and rules.

1.2 Require oversight of pain treatment.

1.3 Provide physician training in pain management and opioid prescribing and establish a residency in pain medicine for medical school graduates.

#2: PRESCRIPTION DRUG MONITORING PROGRAMS (PDMPs)

2.1 Mandate prescriber PDMP use.

2.2 Proactively use PDMP data for enforcement and education purposes.

2.3 Authorize third-party payers to access PDMP data with proper protections.

2.4 Empower licensing boards for health professions and law enforcement to investigate high-risk prescribers and dispensers.

#3: PHARMACY BENEFIT MANAGERS (PBMs) AND PHARMACIES

3.1 Inform and support evaluation research.

3.2 Engage in consensus process to identify evidence-based criteria for using PBM and pharmacy claims data to identify people at high risk for abuse and in need of treatment.

3.3 Expand access to Prescription Drug Monitoring Programs.

3.4 Improve management and oversight of individuals who use controlled substances.

3.5 Support restricted recipient (lock-in) programs.

3.6 Support take-back programs.

3.7 Improve monitoring of pharmacies, prescribers and beneficiaries.

3.8 Incentivize electronic prescribing.

#4: ENGINEERING STRATEGIES

4.1 Convene a stakeholder meeting to assess the current product environment (e.g., products available, evidence to support effectiveness, regulatory issues) and identify high-priority future directions for engineering-related solutions.

4.2 Sponsor design competitions to incentivize innovative packaging and dispensing solutions.

4.3 Secure funding for research to assess the effectiveness of innovative packaging and designs available and under development.

4.4 Use research to assure product uptake.

#5: OVERDOSE EDUCATION AND NALOXONE DISTRIBUTION PROGRAMS

5.1 Engage with the scientific community to assess the research needs related to naloxone distribution evaluations and identify high-priority future directions for naloxone-related research.

5.2 Partner with product developers to design naloxone formulations that are easier to use by nonmedical personnel and less costly to deliver.

5.3 Work with insurers and other third-party payers to ensure coverage of naloxone products.

5.4 Partner with community-based overdose education and naloxone distribution programs to identify stable funding sources to ensure program sustainability.

5.5. Engage with the healthcare professional community to advance consensus guidelines on the co-prescription of naloxone with prescription opioids.

#6: ADDICTION TREATMENT

6.1 Invest in surveillance of opioid addiction.

6.2 Expand access to buprenorphine treatment.

6.3 Require federally-funded treatment programs to allow patients access to buprenorphine or methadone.

6.4 Provide treatment funding for communities with high rates of opioid addiction and limited access to treatment.

6.5 Develop and disseminate a public education campaign about the important role for treatment in addressing opioid addiction.

6.6 Educate prescribers and pharmacists about how to prevent, identify and treat opioid addiction.

6.7 Support treatment-related research.

#7: COMMUNITY-BASED PREVENTION STRATEGIES

7.1 Invest in surveillance to ascertain how patients in treatment for opioid abuse and those who have overdosed obtain their supply.

7.2 Convene a stakeholder meeting with broad representation to create guidance that will help communities undertake comprehensive approaches that address the supply of, and demand for, prescription opioids in their locales; implement and evaluate demonstration projects that model these approaches.

7.3 Convene an inter-agency task force to ensure that current and future national public education campaigns about prescription opioids are informed by the available evidence and that best practices are shared.

7.4 Provide clear and consistent guidance on safe storage of prescription drugs.

7.5 Develop clear and consistent guidance on safe disposal of prescription drugs; expand access to take-back programs.

7.6 Require that federal support for prescription drug misuse, abuse and overdose interventions include outcome data.

Background

In May 2014, a diverse group of experts — including clinicians, researchers, government officials, injury prevention professionals, law enforcement leaders, pharmaceutical manufacturers and distributers, lawyers, health insurers and patient representatives — gathered at the Johns Hopkins Bloomberg School of Public Health. The group gathered to review what is known about prescription opioid misuse, abuse, addiction and overdose; to identify strategies for reversing the alarming trends in injuries and deaths from these drugs; and to make recommendations for action. The group convened at the invitation of the Clinton Foundation and two of the School's centers: the John Hopkins Center for Drug Safety and Effectiveness and the John Hopkings Center for Injury Research and Policy. Prior to the meeting, the School hosted a public town hall meeting during which President Bill Clinton provided an inspiring call to action.

During the day-and-a-half meeting, participants identified opportunities for intervention along the supply chain (including the development and production process, legal and illegal markets, and insurance coverage); and within the clinical, community and addiction treatment settings. The result was a commitment to develop and implement a plan of action that utilizes the multi-disciplinary skills and expertise of the many stakeholders committed to addressing the issue.

In the months that followed this initial gathering, the group divided into work groups to review the available evidence and make recommendations based on that literature. This process was guided by the following principles:

INFORMING ACTION WITH EVIDENCE.

Some evidence-based interventions exist to inform action to address this public health emergency; these should be scaled up and widely disseminated. Furthermore, many promising ideas are evidence-informed, but have not yet been rigorously evaluated. The urgent need for action requires that we rapidly implement and carefully evaluate these promising policies and programs. The search for new, innovative solutions also needs to be supported.

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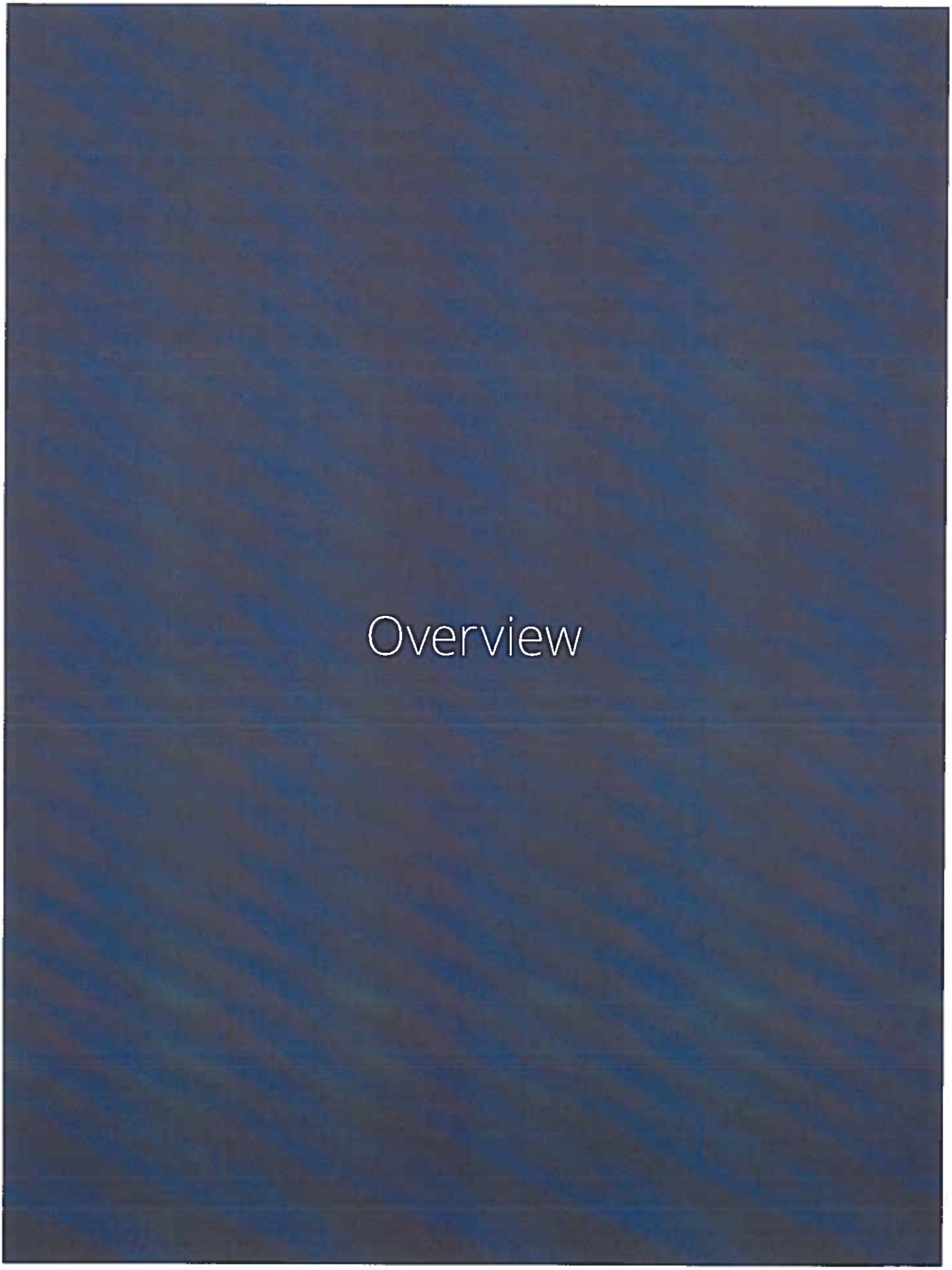
This report is the result of the work group process.


Overview

Prescription drugs are essential to improving the functioning and quality of life for patients living with acute or chronic medical conditions. Although all prescription drugs have some misuse risk, of particular concern is the misuse and abuse of the drugs identified by the Drug Enforcement Administration (DEA) as controlled substances. These products, such as prescription opioids, have high abuse potential and can lead to life-threatening adverse events when taken in excess or in combination with other drugs.[1,2]

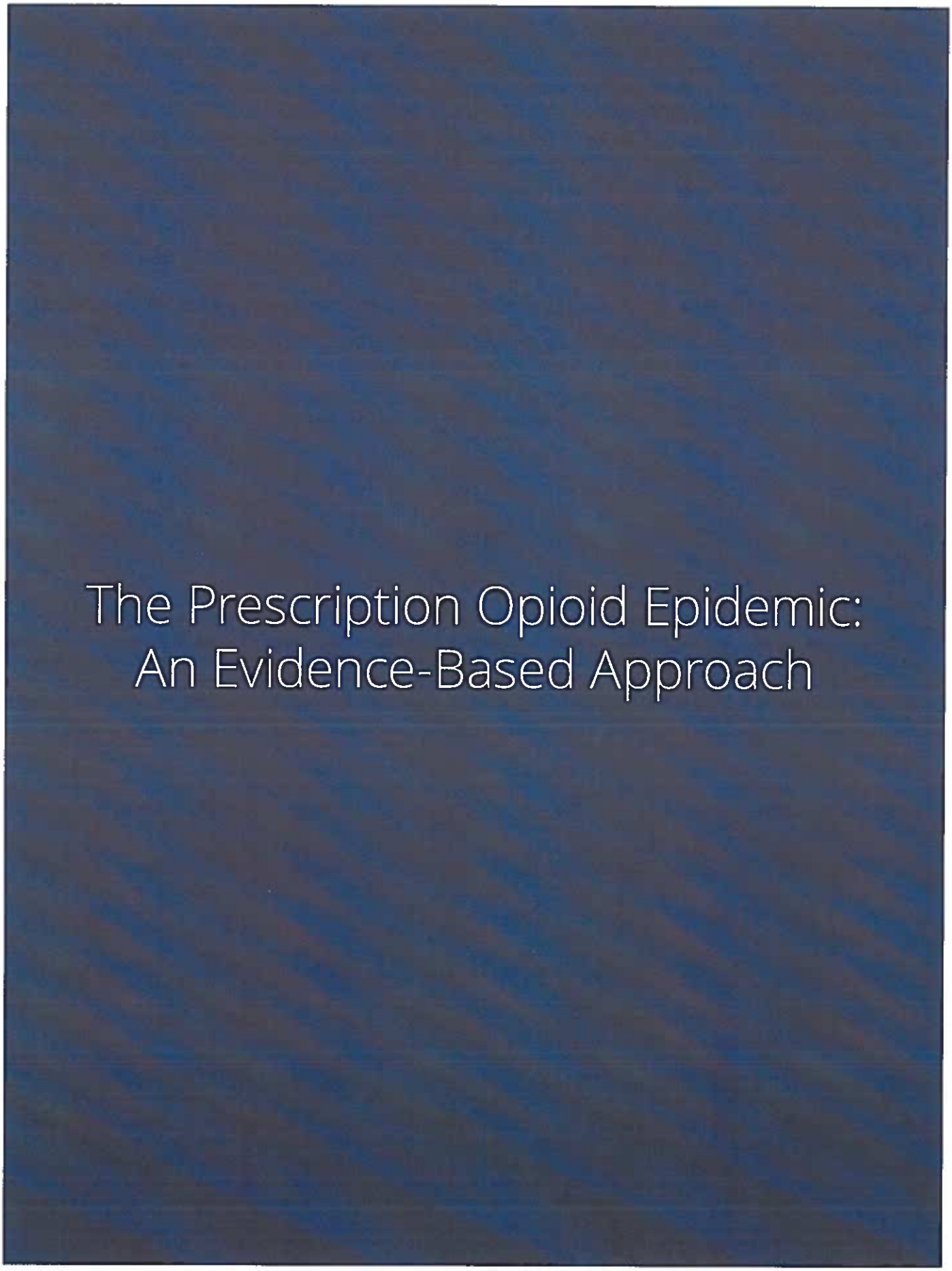
Prescription drug abuse and overdose is a serious public health problem in the United States. Drug overdose death rates in the U.S. increased five-fold between 1980 and 2008, making drug overdose the leading cause of injury death.[3] In 2013, opioid analgesics were involved in 16,235 deaths — far exceeding deaths from any other drug or drug class, licit or illicit.[4] According to the National Survey on Drug Use and Health (NSDUH), in 2012 an estimated 2.1 million Americans were addicted to opioid pain relievers and 467,000 were addicted to heroin.[5] These estimates do not include an additional 2.5 million or more pain patients who may be suffering from an opioid use disorder because the NSDUH excludes individuals receiving legitimate opioid prescriptions.[6]

A public health response to this crisis must focus on preventing new cases of opioid addiction, early identification of opioid-addicted individuals, and ensuring access to effective opioid addiction treatment, while at the same time continuing to safely meet the needs of patients experiencing pain. It is widely recognized that a multi-pronged approach is needed to address the prescription opioid epidemic. A successful response to this problem will target the points along the spectrum of prescription drug production, distribution, prescribing, dispensing, use and treatment that can contribute to abuse; and offer opportunities to intervene for the purpose of preventing and treating misuse, abuse and overdose.

This report provides a comprehensive overview of seven target points of opportunity, summarizes the evidence about intervention strategies for each, and offers recommendations for advancing the field through policy and practice.

#1: Prescribing Guidelines
#2: Prescription Drug Monitoring Programs
#3: Pharmacy Benefit Managers and Pharmacies
#4: Engineering Strategies
#5: Overdose Education and Naloxone Distribution Programs
#6: Addiction Treatment
#7: Community-Based Prevention

The remainder of this report is organized by these seven topic areas.


The Prescription Opioid Epidemic:
An Evidence-Based Approach

STATEMENT OF THE PROBLEM

More than 100,000 people in the United States have died — directly or indirectly — from prescribed opioids since prescribing policies changed in the late 1990's.[7] At that time, patient advocacy groups and pain specialists successfully lobbied state medical boards and state legislatures to change statutes and regulations to lift any prohibition of opioid use for non-cancer pain. In at least 20 states, these new guidelines, statutes, regulations and laws dramatically liberalized the long-term use of opioids for chronic non-cancer pain, reflecting the prevailing thought at the time that there is no clinically appropriate ceiling on maximum opioid dosing.[8] An example of such permissive language can be found in Washington State Administrative code (WAC) 246-919-830 from December 1999, which states: "no disciplinary action will be taken against a practitioner based solely on the quantity or frequency of opioids prescribed."

With the introduction of pain as the "fifth vital sign,"[9] accompanied by pharmaceutical company efforts to market directly to prescribers,[10] there has been a dramatic increase in prescription opioid sales. Studies have documented a strong and consistent linear relationship between opioid sales volume and morbidity and mortality associated with these products.[11]

SYNTHESIS OF AVAILABLE EVIDENCE

As opioid-related deaths continued to accelerate, constituting a national epidemic and public health emergency,[12,13] an increasing number of systematic reviews surfaced assessing the efficacy and effectiveness of opioids for chronic non-cancer pain. These systematic reviews concluded that the overall effectiveness of chronic opioid treatment for chronic non-cancer pain is limited, the effect on improved human function is very small and the safety profile of opioids is poor.[14,15,16] Briefly stated, the evidence on efficacy and effectiveness of these drugs for chronic non-cancer pain has demonstrated:

1. A variety of adverse events associated with opioid use, including: hypogonadism and infertility; neonatal abstinence syndrome; sleep breathing disorders; cardiac arrhythmias; opioid-induced hyperalgesia; and falls and fractures among the elderly;

2. High rates of healthcare utilization associated with these adverse events, including emergency department visits and hospitalizations from non-fatal overdoses;

3. High rates of deaths from unintentional poisonings, especially at doses at or above 100–120 morphine milligram equivalents (MME) per day, which generally occur at home during sleep;

4. Minimal improvement in pain and function associated with long-term opioid use for chronic non-cancer pain; and

5. An overall unfavorable risk/benefit balance for many current opioid users.

The evidence on state policy strategies and their effect on prescribing patterns demonstrates that state governments are willing to promote safe and effective pain management while taking precautions to curtail the alarming increase of opioid related morbidity and deaths.[17] However, policy language varies: Some states emphasize the need to prevent illicit trafficking and drug abuse,[18] while others encourage appropriate pain management while avoiding undue burdens on practitioners and patients.[19] Some states follow the advice of specialty societies. However, position papers of expert groups differ, as does the soundness of their recommendations, including some recommendations under investigation by the U.S. Senate at the time of this writing.[20]

The Washington State experience is particularly informative to prescribing guideline policies. In 2007, the State responded to epidemic opioid-related morbidity and mortality by engaging the public state agencies to collaborate with academic and practicing pain clinicians to promulgate opioid dosing guidelines for the local community. The core recommendation developed was to seek specialty consultation if a patient reaches 120 morphine milligram equivalents (MME) per day without improved pain or function. Many states, as well as the Centers for Disease Control and Prevention (CDC) and the Agency for Healthcare Research and Quality (AHRQ), adopted these guidelines as universal precautions.[2] The Centers for Disease Control and Prevention recently engaged in a comprehensive, evidence-based process to develop guidelines for prescribing opioids for chronic pain. The resulting Guideline will be released early in 2016. (http://www.cdc.gov/drugoverdose/prescribing/guideline.html)

#1 PRESCRIBING GUIDELINES

Following the initial success of these guidelines and an initial "bending of the curve" of mortality among beneficiaries of these agencies,[22] Washington State passed a landmark bill (ESHB 2876) in 2010. The bill mandated that the boards and commissions representing prescribing providers in the state repeal all prior rules governing opioid prescribing and create new ones by 2011. The bill, which received bi-partisan support, required that the new rules must include:

- Dosing criteria;
- Guidance on when and how to seek consultation (including the use of peer-to-peer video conferencing);
- Guidance on the use of a state prescription drug monitoring program (PDMP); and
- Guidance on tracking clinical progress by using assessment tools focusing on pain, mood, physical function and overall risk for poor outcomes.[23]

Lessons learned from the Washington State policy experience:

- Facilitate collaboration among state agencies and medical boards.
- Establish dosing and best practice rules and incentivize those rules.
- Implement an effective prescription drug-monitoring program that includes real-time data.
- Initiate education programs.
- Evaluate the impact of prescribing guideline interventions regularly.

RECOMMENDATIONS FOR ACTION

1.1 REPEAL EXISTING PERMISSIVE AND LAX PRESCRIPTION LAWS AND RULES.

Federal and state agencies, state medical boards and medical societies should work to repeal previous permissive and lax prescription laws and rules.

Rationale: Previous prescription policies, guidelines, statutes and rulings have been too permissive and have contributed to the current opioid epidemic. They require revision.

Current Status: In 2010, Washington State repealed prior rules related to prescribing and ordered new rules promulgated by 2011. State laws on this topic vary. A list of statutes, regulations, and other state policies relevant to opioid prescribing is available from the Pain and Policy Studies Group at University of Wisconsin.[24]

1.2 REQUIRE OVERSIGHT OF PAIN TREATMENT.

Federal and state agencies, state medical boards and medical societies should require mandatory tracking of pain, mood and function through use of a brief validated survey at every patient medical visit; use of patient treatment agreements, urine drug screening; PDMP use when prescribing long-term opioids for non-chronic pain; and specialty consultation (via peer-to-peer video conferencing when in-person is unavailable) when prescribing over 120 morphine milligram equivalents (MME) per day without pain and function improvement.

Rationale: Given the risks associated with prescription opioids, protocols and tools for monitoring them, and decision-making when prescribing them, are needed to improve the safety of prescribing practices.

Current Status: These guidelines have been adopted by Washington State and appear in whole or in part in many other guidelines endorsed by the Department of Defense (DoD), Veteran's Administration (VA), and the AHRQ, as well as by professional societies like the American College of Occupational and Environmental Medicine (ACOEM), American Pain Society (APS), American Academy of Pain Medicine (AAPM), and American Society of Interventional Pain Physicians (ASIPP). A comparative table of guideline recommendations published by the CDC has been published.[25]

1.3 PROVIDE PHYSICIAN TRAINING IN PAIN MANAGEMENT AND OPIOID PRESCRIBING AND ESTABLISH A RESIDENCY IN PAIN MEDICINE FOR MEDICAL SCHOOL GRADUATES.

Federal and state agencies, state medical boards, and medical societies should assure pre-graduate and post-graduate training in pain management and opioid prescription, including: continuing medical education (CME); graduate medical education (GME); post graduate education; and creation of a full three-year residency training program in pain medicine, which currently does not exist.

Rationale: Training in pain management is needed in order to move toward more effective, less risky treatments. An estimated 10,000 pain specialists cannot meet the treatment needs of the millions of chronic pain sufferers in the U.S.

Current Status: The American Association of Medical Colleges (AAMC) has endorsed efforts to increase the instruction of pain medicine in medical schools, however standards have not yet been defined. There is no full three-year residency training program in pain medicine in the U.S., and although legislation to support such a residency has been proposed and endorsed by leadership of the American Medical Association, it has been refused by the American Board of Medical Specialties.[26] Accredited post-graduate fellowship training in pain medicine is available only for specialists in select fields, such as anesthesiology, neurology, psychiatry and rehabilitation medicine and not for general practitioners or specialists in family or internal medicine. Also available are continuing medical education (CME) courses, generally sponsored by pharmaceutical manufacturers, through the FDA's Risk Evaluation and Mitigation Strategies (REMS).

#2 PRESCRIPTION DRUG MONITORING PROGRAMS

STATEMENT OF THE PROBLEM

Prescription Drug Monitoring Programs (PDMPs) collect data regarding controlled substances prescriptions from in-state pharmacies and, for most PDMPs, mail order pharmacies that ship prescriptions into the state. There are 51 PDMPs, in all states except Missouri, plus the District of Columbia and Territory of Guam. Through online access to their state's database, physicians and other prescribers can obtain clinical information regarding their patients' controlled substance prescriptions to inform treatment decisions. Typically, information available through the PDMP includes drug name, type, strength and quantity of drugs from previous prescriptions. Physicians and prescribers can also identify patients who may need substance abuse treatment. Similarly, pharmacists can access PDMP data prior to dispensing a controlled substance prescription. These programs are valuable tools to improve patient safety and health outcomes.

PDMPs are under-utilized by prescribers. More than a quarter (28 percent) of primary care physicians in one study reported not being aware of their states' PDMPs.[27] While a majority of clinicians (53 percent) reported having obtained data from their PDMP at some point, data are accessed in fewer than a quarter of the instances when these physicians prescribed an opioid. Performance measures reported by 17 states for the first quarter of 2012 indicate that the median percent of prescribers who issued controlled substance prescriptions who registered to use their states' PDMPs was 31 percent,[28] and the median number of reports requested by all prescribers who issued one or more controlled substance prescriptions was 3.28. Even the highest rates of PDMP registration did not ensure use. For example, during the first quarter of 2012, Kentucky had the fifth highest proportion of registered prescribers at 49 percent,[28] yet prescribers and pharmacists requested information for only 6 percent of 2.9 million controlled substance prescriptions dispensed.[29] Physicians identify a number of barriers to PDMP use, including that retrieving the information is too time consuming and difficult.[30]

This underutilization of PDMPs is particularly troubling because PDMPs can help identify persons who may be engaged in high-risk behavior, such as doctor shopping and prescription forgery, indicating possible abuse of or dependence on controlled substances. PDMP data can be used to alert health care professionals if a patient is at risk for addiction or overdose, since certain indicators are known risk factors for high-risk utilization. For example, persons who doctor shop are seven times more likely to die of opioid overdoses than persons who do not; those who pharmacy shop are more than 13 times more likely to suffer an overdose death.[31] People who ingest 100 milligrams of morphine milligram equivalents or more per day have an almost nine-fold increase in overdose risk.[32]

SYNTHESIS OF AVAILABLE EVIDENCE

In response to the problem of inadequate utilization of PDMPs described above, state lawmakers and PDMP administrators have made several adjustments, including:

- Authorization of delegates (approved clinical professionals) to request PDMP data. As of 2014, 36 states had laws authorizing delegates to request PDMP data.
- Establishment of interoperability with electronic health records and the Affordable Care Act's health information exchanges. The Substance Abuse and Mental Health Services Administration (SAMHSA) is providing grants to support this work in 16 states.[33, 34]
- Proactive analysis of PDMP data and forwarding of unsolicited reports to prescribers and pharmacists; when these professionals receive unsolicited reports from PDMP administrators, they increase their own data requests.[35, 36]
- Increased speed of data collection. Twenty-two states require pharmacies to submit data daily, 27 collect data on a weekly basis or less, and one collects data bi-weekly. By June 30, 2015, only one state remains at the old standard of monthly data submission.
- Increased interstate PDMP data sharing so prescribers can observe prescriptions dispensed in other states; 28 states[37] are engaged in interstate data sharing and others are working toward these agreements.

States, faced with low prescriber utilization, are increasingly mandating that prescribers use PDMPs. Sixteen states[38, 39] mandate that prescribers use PDMPs under certain circumstances; an additional 11 states have comprehensive mandates as of December 2014.[40, 41] Kentucky was the first state to mandate comprehensive PDMP use. Prescribers' PDMP use increased following the mandate, and decreases in opioid prescribing, doctor shopping and prescription overdose hospitalizations were noted in a 2015 evaluation — although heroin treatment admissions rose during the study period.[42]

Additional information about the Kentucky law and the impacts measured to date follow.

- Prescribers must review PDMP data prior to issuing a patient's first opioid prescription, and at least every three months thereafter for continued therapy and new or refill opioid prescriptions, with some exceptions. This requirement went into effect in July 2012. The 2015 evaluation found that the mean number of prescribers' requests increased by 650 percent annually compared to the period prior to the law's effective date.[43, 44]
- Prior to the mandate, Kentucky clinicians' report requests had increased by about 85,000 reports annually. At that rate it would have taken approximately 38 years to reach the level achieved within three months of the new law. [45]
- Opioid prescriptions decreased by 8.6% in the year following implementation of the law.[3]
- According to data provided by the Kentucky Office of Drug Control Policy, from 2011 to 2013, overdose hospitalizations due to prescription opioids declined by 26 percent, emergency department visits related to prescription opioids declined by 15 percent,[46] and prescription opioid deaths declined by 25 percent, the first declines in 10 years.[47]

Like Kentucky, other comprehensive mandate states (Tennessee, New York, Ohio) experienced rapid increases in PDMP registrations, increases in PDMP data use (up to 10,000 percent in New York),[48] decreases in prescribing commonly abused controlled substances, and decreases in multiple provider, or "doctor-shopping" episodes.

Additional professional groups that could use PDMP data to intervene and interrupt harmful prescription-controlled substance behaviors include:

Third-party healthcare payers and their pharmacy benefit managers (PBMs) that have the ability to intervene with prescribers, dispensers and patients. Medicaid programs and some of the private third-party payers use Patient Review and Restriction (PRR), such as "Lock-in". Typically, these programs restrict high-risk patients to one doctor and one pharmacy for the controlled substance prescriptions. These programs can effectively protect patient health and safety as well as prevent program fraud, especially when augmented by access to PDMP data.[49, 50]

Professional licensing boards that oversee clinicians and have an interest in identifying who is abusing controlled substances and/or who has high-risk prescribing or dispensing patterns. Recent findings identify a small number of prescribers as responsible for a disproportionate number of opioid prescriptions.[51] Oregon's PDMP found that the top 4 percent of prescribers issued 60 percent of all controlled substance prescriptions.[52] In New York City, 1 percent of prescribers wrote 31 percent of opioid prescriptions. A large chain pharmacy found 42 outlier prescribers out of more than 1 million. Within that chain alone, the 42 each issued prescriptions for about 5,000 average monthly doses of high-risk drugs over 21 months. On an annual basis that would cumulatively total more than 4 million dosage units.[53]

Law enforcement agencies that can identify possible criminal activity, such as "doctor shopper" rings and pill mills. Jung, et al found that among 47 physicians arrested by the Drug Enforcement Agency (DEA) in 2003 and 56 whose DEA registrations were revoked in 2003–2004, there was not sufficient information in the majority of cases to confirm the existence of a documented doctor/chronic pain patient relationship.[54]

Public health agencies that provide an early warning system for communities about the risks of opioid overdoses and deaths. PDMP data can also be analyzed at the county and community level within a short time of actual prescription dispensing and provide warnings to states and communities of the risk of increasing opioid overdoses and deaths. The Prescription Behavior Surveillance System (PBSS) was developed by the PDMP Center of Excellence (COE) in conjunction with the National Center for Injury Prevention and Control (NCIPC) and the Food and Drug Administration (FDA) to help identify communities at risk for harmful opioid outcomes. A variety of measures — such as mean daily dosage of opioids per patient, multiple provider episode rates, percentage of days with overlapping prescriptions for opioids and benzodiazepines and median distance in miles from patient to prescriber — can be tracked and followed over space and time.[55] By using PDMP data for public health surveillance, states and communities can monitor prescribing trends.[56] In turn, they can take actions to protect against opioid addiction, overdoses and deaths, as demonstrated by Project Lazarus in North Carolina.[57] Given the limited resources available to states and communities, this type of information is essential for targeting prevention and other resources to areas of greatest need, according to substance abuse prevention specialists and others.[58]

#2 PRESCRIPTION DRUG MONITORING PROGRAMS

RECOMMENDATIONS FOR ACTION

2.1 MANDATE PRESCRIBER PDMP USE.

Through regulation or legislation, states should mandate prescriber use of PDMPs in order to achieve more comprehensive and effective use of PDMP data in treating patients.

Rationale: Mandatory PDMP use policies are associated with increased use.[59]

Current Status: Sixteen states mandate that prescribers use PDMPs under certain circumstances; an additional seven states have comprehensive mandates.

2.2 PROACTIVELY USE PDMP DATA FOR ENFORCEMENT AND EDUCATION PURPOSES.

States should analyze their PDMP data to identify: 1) potential inappropriate or illegal activities and forward the information in unsolicited reports to the relevant professional groups to increase oversight of controlled substance prescribing; and 2) hot spots of inappropriate and/or illegal use so that prevention efforts are data-driven and evidence-informed. Primary recipients of PDMP data reports should include prescribers, dispensers, professional licensing boards, law enforcement agencies, and state and community prevention and treatment programs.

Rationale: Many PDMPs underutilize the data and do not engage in proactive reporting, nor do they participate in PBSS or state-based equivalent reporting. Better use of PDMP data will aid identification of opportunities for intervention, and prevent misuse, abuse and overdose through enforcement and education.

Current Status: Twenty-eight states[60] engage in proactive data analysis and reporting activities as of 2014. Only four states provide unsolicited reports to all four primary recipient groups (prescribers, dispensers, professional licensing boards and law enforcement agencies).[61]

Twelve states[62] participate in PBSS by sending de-identified PDMP data to and receiving reports from the Brandeis PDMP Center of Excellence (COE). The CDC and FDA fund the project through an agreement with the Bureau of Justice Assistance.[63] States not participating in PBSS can initiate their own data analysis and sharing with state and community prevention and treatment programs.

2.3 AUTHORIZE THIRD-PARTY PAYERS TO ACCESS PDMP DATA WITH PROPER PROTECTIONS.

States should authorize Medicaid, Medicare, the Veterans Administration, Department of Defense, Indian Health Service, workers compensation carriers and private third-party healthcare payers to access PDMP data for their enrollees, with proper protections. The authorization should also allow Pharmacy Benefit Managers (PBMs) (See Section 3 of this report for more information on PBMs) to access the data as agents of the third-party payers for whom they manage benefits.

Rationale: Such access can provide third-party payers with valuable information to inform internal policies that address the misuse, abuse and overdose associated with controlled substance prescriptions.

Current Status: Thirty-two states and one territory[64] authorize some combination of third-party payers to access PDMP data. Only five states provide access to Medicare and three states[65] to commercial third-party payers. States should consider the Washington State model that authorizes Medicaid and Workers Compensation to access the PDMP data in bulk.[66]

2.4 EMPOWER LICENSING BOARDS FOR HEALTH PROFESSIONS AND LAW ENFORCEMENT TO INVESTIGATE HIGH-RISK PRESCRIBERS AND DISPENSERS.

All states should direct their PDMPs to proactively analyze these data to identify possible misconduct and criminal activities and to provide the information unsolicited to licensing boards and law enforcement in order to develop and inform investigations.

Rationale: Licensing boards need access to PDMP data to investigate possible misconduct involving controlled substances. Authority to enforce controlled substance laws is the responsibility of federal, state and local law enforcement. Law enforcement should have access to PDMP data in order to inform this authority.

#2 PRESCRIPTION DRUG MONITORING PROGRAMS

Current Status: Forty-six states, Guam, and the District of Columbia permit their licensing boards to access PDMP data; three states do not.[67] Eleven states send unsolicited reports to licensing boards.[68]

Three states[69] report they permit specially trained investigators to directly access PDMP data on-line. Thirty states[70] require probable cause, search warrants, subpoenas or other judicial processes in order for law enforcement officers to access data. One state does not authorize law enforcement officers to have access. Seventeen states proactively analyze and send unsolicited reports to law enforcement agencies.[71]

#3 PHARMACY BENEFIT MANAGERS (PBMs) AND PHARMACIES

STATEMENT OF THE PROBLEM

PBMs and pharmacies possess different types of data that are relevant to reducing prescription drug abuse and diversion. Since PBMs manage the pharmacy benefits for health plans and large employers, they possess members' claims data for prescription drugs, and at times, other healthcare goods and services. PBMs do not have visibility of prescriptions paid with cash or those paid by another insurer. Pharmacies, on the other hand, only possess information about a patient's prescriptions if the patient filled his or her medicine with that pharmacy or pharmacy chain. The fact that PBMs and pharmacies may lack a comprehensive view of an individual patient's prescription history is one reason that it is essential for state-run prescription drug monitoring programs (PDMPs) to have comprehensive controlled substances information for an individual, and for this information to be shared with payers, as well as with other states. As described in Section 2 of this document, PDMPs can have comprehensive controlled substances prescription records for an individual regardless of whether the individual paid cash or filled prescriptions through multiple insurers and pharmacies. However, not all insurers/PBMs are allowed to access the PDMP information, nor are PDMPs comprehensively interconnected among all states.

SYNTHESIS OF AVAILABLE EVIDENCE

There are many methods that PBMs and pharmacies can use to reduce inappropriate prescribing and to intervene upon individuals likely to be abusing or diverting prescription drugs.[72, 73, 74] Evidence of the impact of PBMs' procedures and programs has been summarized.[75, 76] Importantly, as pointed out by Haegerich and colleagues in their report on studies of state policy or systems-level interventions to prevent drug misuse and abuse,

> *"Overall study quality is low. Knowledge and prescribing practices were measured more often than health outcomes (e.g., overdoses). Limitations include lack of baseline data and comparison groups, inadequate statistical testing, small sample sizes, self-reported outcomes, and short-term follow-up. Evidence of improved health outcomes, particularly from safe storage and disposal strategies and patient education, is weak."*[73]

Many PBMs perform prescription claims reviews using software algorithms to identify individuals, pharmacies and prescribers that are potentially fraudulently using or dispensing controlled substances. In addition, PBMs' prescription claims surveillance and prescriber intervention programs often use retrospective analysis to identify members meeting excessive controlled substance use criteria, such as some combination of the use of multiple prescribers, multiple dispensing pharmacies, exceeding a threshold of morphine milligram equivalent (MME) dose, and multiple controlled substance claims over a period of three to six months. Most PBMs' internal controlled substance claim surveillance criteria are not disclosed or validated to be associated with controlled substance adverse events, mortality, health care utilization or costs. However, some criteria used by PBMs have been published.[77, 78] Prescriber letter interventions through PBMs have been shown to decrease members' controlled substance score and controlled substance drug claims.[79, 80] These programs could be enhanced if the PBM has complete controlled substance claims history, including cash claims, through access to states' PDMPs.

Examples of PBMs' controlled substances utilization management programs include prior authorization, precertification and maximum quantity limits per prescription. The health insurer Aetna reported in 2014 that its PBM "Pharmacy Misuse, Waste and Abuse" program monitors access to opioids through precertification and reviews of pharmacy and medical claims and quantity limits to find patterns of above-normal use. Further, members who have had frequent emergency room visits are identified. Other signs, and suspicion of developing substance abuse problems or a history of controlled substance abuse, also are noted. The program reduced opioid prescriptions among 4.3 million members by 14 percent between January 2010 and January 2012.[81]

An Aetna-run Behavioral Health Medication Assistance Program involves nurses and psychologists working with physicians to evaluate members who could be at risk for addiction and those with a history of opioid abuse or who are in treatment. According to Aetna, this program has shown "a 30 percent improvement in opioid abstinence rates; a 35 percent reduction of in-patient hospital admissions and a 40 percent decrease in total paid medical costs."[82] Blue Cross Blue Shield of Massachusetts reported in 2014 that its program implemented in July 2012 to require a prior authorization for more than 30 days of opioid therapy reduced prescriptions by 20 percent for common opioids such as Percocet (oxycodone and acetaminophen) and 50 percent for longer-acting drugs such as OxyContin (extended-release oxycodone), and cut total prescriptions of narcotic painkillers by an estimated 6.6 million pills in 18 months.[83]

For patients who have particularly high-risk controlled substance use and whose utilization cannot be safely addressed using other mechanisms, insurers or PBMs may enroll the member in a pharmacy and/or prescriber restriction program. These

programs, also known as "lock-in" programs, are applied to fewer than 1 in 1,000 controlled substance-using individuals, and have been used by state Medicaid programs for years. Restricted recipient programs limit an individual to receiving their controlled substance prescriptions from one prescriber and one pharmacy for allowed insurance payment, or else the individual must pay cash. As stated by the Academy of Managed Care Pharmacy:

> *"Prescriber and pharmacy restricted access programs help to mitigate the issues associated with doctor or pharmacy shopping and may reduce the number of inappropriate controlled substance prescriptions. In 2009, the Oklahoma Medicaid department found that its lock-in program reduced doctor shopping, utilization rates of controlled substances, and emergency room visits with a savings of $600 per person in costs. As demonstrated in Medicaid and other programs and recommended by the General Accountability Office in 2011, to reduce incidence of doctor or pharmacy shopping, a common way that Medicare beneficiaries obtain inappropriate controlled substances, CMS should consider restricted access to certain prescribers and pharmacies for Medicare beneficiaries."* [84, 85]

Formulary controls are also used by PBMs to guide patients and prescribers toward the safest, most cost effective medications and then to cover these drugs at a lower member cost share to encourage their use. Exclusion of a controlled substance drug from a formulary results in the drug not being covered by the insurance policy. For example, the product Zohydro ER has been excluded from some formularies due to concerns about its potential for abuse and overdose. Minnesota Medicaid chose to exclude promethazine with codeine syrup and carisoprodol beginning in 2015 due to the potential for concomitant abuse of these three drugs and insufficient evidence to support their clinical benefit when used together.[86] Research is needed to understand the impact of these types of policies.

Pharmacies can also remove prescriber dispensing privileges to curtail both diversion and inappropriate controlled substance prescribing, and they can require pharmacists to provide patient counseling to help those with controlled substance dependence.[87, 88, 89] The removal of prescriber dispensing privileges to curtail both diversion and inappropriate controlled substance prescribing is feasible and supported by state and federal law.[90] With the goal of ensuring that prescriptions for controlled substances are appropriate, one pharmacy chain identified 42 controlled substance outlier prescribers out of more than 1 million prescribers. After allowing for appeal, 36 prescribers had their prescriber dispensing privileges removed,[91] reducing more than 100,000 doses of high-risk drugs prescribed per month.

Electronic prescribing (e-prescribing) is the process by which a prescriber generates and transmits an "accurate, error-free and understandable" prescription directly to a pharmacy through a special secure network. E-prescribing for controlled substance drugs has the potential to reduce forgery and fraudulent controlled substance prescriptions.[92] Research indicates that few controlled substance prescriptions are e-prescribed.[93] It is anticipated that e-prescribing will soon become commonplace, especially with new laws like New York's iSTOP law. The e-prescribing requirements were a part of the State's Internet System for Tracking Over Prescribing (I-STOP) laws, enacted in 2012. I-STOP requires all prescribers to: 1) consult the Prescription Monitoring Program (PMP) prior to prescribing Schedule II, III and IV controlled substances and 2) electronically transmit all prescriptions. Evaluations to monitor the impact of such initiatives will be critical to maximizing the use of e-prescribing as a tool for more effectively controlling the supply of controlled substances.

The Drug Enforcement Administration (DEA) and state boards of pharmacy require pharmacists to use sound professional judgment when determining whether or not to fill controlled substance prescriptions. After reviewing the prescription, pharmacists will use their professional judgment on handling any issues that may come up. This professional activity is enhanced through pharmacist access to and use of PDMPs to review a member's claims history in questionable cases. Interstate PDMP data access with infrastructure supporting high utilization and rapid response times is essential to ensure that PDMP data are optimally used by prescribers and pharmacists.[94]

Although they have not yet been widely enacted, "take-back" programs that foster safer medication disposal by allowing for patients to return unused or unwanted opioids may also help to reduce the potential for diversion of opioids and other controlled prescription drugs from licit to illicit channels. Pharmacies provide a convenient site for individuals to dispose of their unused controlled substance prescriptions. Evidence supporting the effectiveness of allowing pharmacies to take back and destroy prescription drugs is anecdotal. Additional discussion of this strategy is included in Section 7 of this report.

#3 PHARMACY BENEFIT MANAGERS (PBMs) AND PHARMACIES

RECOMMENDATIONS FOR ACTION

3.1 INFORM AND SUPPORT EVALUATION RESEARCH.

Pharmacies and PBMs are engaged in controlled substance interventions. Research funded by the federal government, non-profit and for profit entities is needed to evaluate the clinical and economic impact of these efforts. A stakeholder meeting to review research that is in progress and to identify priorities for new research is needed to inform investment in this area.

Rationale: Without high quality evaluations of interventions, pharmacies and PBMs will lack a reliable evidence base to inform how best to invest prevention dollars.

Current Status: The Patient-Centered Outcomes Research Institute (PCORI) has no funded projects. The Centers for Disease Control and Prevention (CDC) and the National Institute on Drug Abuse (NIDA) have sponsored modest extramural funding in this realm. The private sector is conducting research, much of which goes unpublished. We are unaware of any other funding sources active in this area.

3.2 ENGAGE IN CONSENSUS PROCESS TO IDENTIFY EVIDENCE-BASED CRITERIA FOR USING PBM AND PHARMACY CLAIMS DATA TO IDENTIFY PEOPLE AT HIGH RISK FOR ABUSE AND IN NEED OF TREATMENT.

This can be accomplished through a consensus process that brings together experts in the field to identify criteria to include.

Rationale: Criteria currently in use to identify individuals at high risk for abuse or overdose requires further validation and refinement. It is essential that scientific evidence be applied to reduce false positive or false negative identification.

Current Status: State Medicaid, managed care plans and PBMs are using varying methods with varying degrees of evidence to support them.

3.3 EXPAND ACCESS TO PDMP.

Amend state PDMP laws to allow managed care plans and PBMs access to PDMPs to ensure complete claims history for covered members. These laws must include proper protections for patient privacy.

Rationale: Allowing managed care plans and PBMs access to PDMP data will improve upon their current controlled substances interventions that have been shown to positively influence controlled substances utilization.

Current Status: PDMP legislation generally prohibits managed care plans and PBMs from accessing PDMP data. State legislatures will need to change their state PDMP laws to allow managed care plans and PBMs access to data.

3.4 IMPROVE MANAGEMENT AND OVERSIGHT OF INDIVIDUALS WHO USE CONTROLLED SUBSTANCES.

Encourage the states and Centers for Medicare & Medicaid Services (CMS) to incentivize PBMs, through the Medicaid Innovation Accelerator Program and CMS Innovation Center, to implement and rigorously evaluate innovative medication management strategies for targeted management of individuals who use controlled substances.

Rationale: Managed care plans and PBMs are uniquely positioned to efficiently aggregate data and take action.

Current Status: A systematic assessment of how plans and PBMs are currently implementing and evaluating management and oversight of individuals who use controlled substances does not exist.

3.5 SUPPORT RESTRICTED RECIPIENT (LOCK-IN) PROGRAMS.

The federal government should amend the Medicare Part D to allow prescriber and pharmacy restricted recipient (lock-in) programs.

Rationale: Demonstrated success with the Medicaid restricted recipient programs should be shared with legislators to inform them of the opportunity to prevent opioid abuse in Medicare.

Current Status: Prescriber and pharmacy restricted recipient programs are legislatively prohibited in Medicare. Federal legislators will need to change the Medicare Part D law to allow managed care plans and PBMs to implement prescriber and pharmacy restricted recipient programs.

3.6 SUPPORT TAKE-BACK PROGRAMS.

Pharmacies should encourage their patients to return unused controlled substances.

Rationale: Pharmacies are a convenient site for individuals to dispose of their unused controlled substance prescriptions.

Current Status: Some pharmacies are taking back controlled substances. However, pharmacies are not universally providing this service or advertising this service to their patients. Whether the public is aware of the need to properly dispose of these medications is unknown.

3.7 IMPROVE MONITORING OF PHARMACIES, PRESCRIBERS AND BENEFICIARIES.

All PBMs should provide a list of suspicious pharmacies, prescribers and beneficiaries to the National Benefit Integrity Medicare Drug Integrity Contractor (NBI MEDIC). Using the actionable PBM data they are receiving, MEDICs should be reporting potential providers for removal to the CMS.

Rationale: Most PBMs are providing a list of suspicious pharmacies, prescribers and beneficiaries to NBI MEDIC.

Current Status: To our knowledge, CMS is not systematically using the PBM data to exclude providers from being covered and reimbursed by CMS.

3.8 INCENTIVIZE ELECTRONIC PRESCRIBING.

Encourage private insurers and the CMS to incentivize electronic prescribing for controlled substances.

Rationale: E-prescribing for controlled substance drugs has the potential to reduce forgery and fraudulent controlled substance prescriptions.

Current Status: Although controlled substances e-prescribing is infrequent as of this writing, the expectation is that e-prescribing will increase with new state laws and electronic medical record connectivity with pharmacies.

#4 ENGINEERING STRATEGIES: PRESCRIPTION DRUGS AND PACKAGING

STATEMENT OF THE PROBLEM

Although prescription drug abuse is a complex, multi-faceted issue, the data strongly indicate that the vast majority of prescription drugs that are abused come from legitimate prescriptions.[95] However, once they are dispensed, prescription drugs are frequently diverted to people using them for nonmedical purposes.[96] Indeed, approximately 70 percent of people who report nonmedical use of prescription opioid pain relievers state they got their most recently used drug from a friend or family member.[97] One component of a comprehensive approach to the problem is to leverage engineering strategies to inform the development of innovative packaging for prescription drug dispensing that can reduce nonmedical use and diversion.

The concept of engineering solutions to improve product safety is a cornerstone of injury prevention. Research indicates that changing products to make them safer is often more effective at reducing injury and death compared to trying to change personal behaviors.[98] Successful examples that have resulted in reductions in morbidity and mortality include the introduction of child-resistant caps to reduce pediatric poisonings; and reductions in motor vehicle crash deaths after mandatory implementation of collapsible steering wheels, energy-absorbing vehicle frames and other physical modifications to motor vehicles.[99, 100, 101, 102] These product-oriented approaches can serve as a model for engineering solutions for prescription drug abuse.

SYNTHESIS OF AVAILABLE EVIDENCE

The U.S. Food and Drug Administration (FDA) highlighted the potential for innovative packaging solutions to be a part of the Agency's response to prescription drug abuse when it published a notice for public comment in the Federal Register in April 2014. The FDA stated that designs for drug packaging have evolved significantly in the past decade and now include many technology-based features — such as electronic systems for monitoring, accessing and improving adherence to medication regimens — that also could help to prevent prescription drug abuse and diversion. Examples of design strategies mentioned by the FDA include: systems that remind patients to take a dose, track when a dose is taken, and limit further access until the next dose is due; radio-frequency identification-based systems; and microchips embedded within tablets. Often these technologies are packaged with data capture systems to provide feedback to providers on adherence, use and potentially tampering.[103]

Although most prescription drug packaging solutions have been designed to improve medication compliance among patients using non-controlled substances for chronic conditions [104, 105], these solutions could be adapted to help prevent prescription drug abuse and diversion. For example, these products could reduce serious complications such as overdose by facilitating appropriate dosage and administration, and could help providers monitor for signs of abuse or diversion. In addition, products that limit access to the medication during non-dosing periods could help prevent use of the medication by someone for whom it was not prescribed. The concept of personalization, i.e., use of a personal identification number, radio-frequency device, fingerprint or other biometrics, has been proposed to prevent other types of injuries [106] and could be applied to prescription drug packaging as well. An example is a pill dispenser that requires a specific fingerprint before releasing the appropriate pain medication at the appropriate time.

Data on the effectiveness of packaging designs on prescription drug abuse is limited. One study of 37 individuals assessed the impact of an electronic medicine dispenser on diversion of buprenorphine-naloxone among patients receiving the drug for opioid addiction treatment. The researchers found 68 percent of patients preferred to use the electronic dispenser to store their tablets compared to the traditional prescription container; 16 percent stated that the dispenser had prevented them from diverting their buprenorphine; 23 percent stated the dispenser prevented others from diverting their buprenorphine; and 58 percent believed the dispenser could prevent diversion. Additionally, 19 percent stated that it was difficult to tamper with the dispenser and 58 percent stated it was impossible to tamper with the dispenser.[107] Another product, which couples a flow-controlled, tamper-resistant medication dispenser with a Web and phone accessible treatment portal, has demonstrated sufficient promise to obtain funding from the National Institute on Drug Abuse. A phase II randomized controlled trial will assess use of the device and opioid misuse among patients from two pain management clinics.[108] However, results from this trial were not available as of June 2015.

A review of the currently available and in-development opioid packaging designs by Lehigh University concluded that many of the commercialized technologies such as locking caps, tamperproof packages and pill-dispensing products are most likely to deter unintentional misuse by elderly people or children and have limited abilities to prevent intentional abuse. However, newer technologies, such as radio-frequency identification wireless technologies and simple technologies combined with radio-frequency identification — as well as other types of smart technologies — have the potential to play a role in deterring intentional opioid abuse by increasing communication between healthcare professionals and patients.[109] As part of their senior mechanical

engineering design course, students at Johns Hopkins University successfully created a prototype of a new design that is tamper-resistant, personalized with fingerprint technology and programmed to deliver a one-month supply of an opioid in the right time and dosage. Only a pharmacist would be able to open and lock the device.[110]

Despite the very limited data on effectiveness, there are a number of products currently being marketed to consumers. There is a pressing need for research to understand the impact of these products on prescription drug abuse. In addition to research questions on effectiveness, there are a number of outstanding questions that need to be explored before widespread adoption of these products can occur. These questions include:

- Where will these products enter the medication prescribing and use process? Will they be made available for purchase by patients for use in their homes? Will pharmacists use them instead of traditional pharmacy dispensing vials? Will manufacturers move away from bulk product distribution and incorporate these packaging designs for direct dispensing from the doctor's office or pharmacy?
- How will these products be regulated? As consumer products? As medical devices? As a combination drug-device?
- Who will take on the costs for these products? Pharmacies? Patients? Insurers/PBMs?
- Who will control, monitor and have access to the data available from these devices?

RECOMMENDATIONS FOR ACTION

4.1 CONVENE A STAKEHOLDER MEETING.

Work with the FDA to convene a meeting with product developers and key stakeholders to assess the current product environment (e.g., products available, evidence to support effectiveness, regulatory issues) and identify high priority future directions for engineering-related solutions.

Rationale: Engineering solutions to deter nonmedical use of prescription opioids are promising and under development. There is a need for coordination of and support for the current efforts to ensure this line of innovation is adequately supported, quickly brought to market and rigorously evaluated.

Current Status: There is no national organizing effort underway; the FDA could promulgate rules or guidance to industry that will affect these innovations and the FDA is a logical stakeholder to convene a meeting or to serve as a partner to convene such a meeting.

4.2 SPONSOR DESIGN COMPETITIONS.

Partner with stakeholders to develop design competitions to incentivize innovative packaging and dispensing solutions.

Rationale: Design competitions have been used to encourage and support innovation in many areas. Engineering strategies for prescription packaging are a logical candidate for such a competition.

Current Status: We are unaware of any design competitions on this subject.

4.3 SECURE FUNDING FOR RESEARCH TO ASSESS THE EFFECTIVENESS OF INNOVATIVE PACKAGING AND DESIGNS AVAILABLE AND UNDER DEVELOPMENT.

Rationale: Data on the effectiveness of packaging interventions is limited. Research is needed to evaluate the engineering innovations under development and to inform future development.

Current Status: We are unaware of any funding source dedicated to evaluating engineering designs for prescription packaging.

4.4 USE RESEARCH TO ENSURE PRODUCT UPTAKE.

Engage with key stakeholders, such as product developers, drug manufacturers, pharmacies, payers, regulators, chronic opioid therapy patients and the public to explore potential barriers and incentives to product uptake, including a tiered reimbursement structure based on packaging designs with demonstrated effectiveness.
Rationale: Innovations in prescription packaging are promising, but little is known about how to ensure the public will use these products and that the products will be integrated into existing payment policies. Research is needed to ensure that these aspects of translation are understood.

Current Status: We are unaware of any efforts to gather empirical data about how to ensure innovative engineering packaging for prescriptions is effectively integrated into the consumer market.

#5 OVERDOSE EDUCATION AND NALOXONE DISTRIBUTION PROGRAMS

STATEMENT OF THE PROBLEM

Naloxone has been used for many years by healthcare and emergency medical services providers to reverse the potentially fatal respiratory depression associated with opioid overdoses. Community-based overdose education and naloxone distribution (OEND) programs that provide naloxone and train at-risk individuals and their friends, family members or caregivers on overdose prevention and response have been implemented in the U.S. in recent years. As of July 2014, at least 644 sites were in existence in the U.S.[111] In addition, some healthcare providers co-prescribe naloxone to patients taking high doses of opioids or to patients who are otherwise at risk for opioid overdose. However, there is limited evidence about the effectiveness of these applications of naloxone, and questions with regard to the sustainability of distribution programs remain, since third-party payers do not universally reimburse for naloxone.

SYNTHESIS OF AVAILABLE EVIDENCE

The majority of the available evaluations of OEND programs report on program implementation; training lay persons to recognize and respond to an overdose event, including the administration of naloxone; and provide information on the number of individuals trained, number of naloxone vials distributed and the number of overdose reversals reported by individuals who were trained.

The settings for OEND evaluations have primarily been in large urban center syringe exchange or harm reduction programs, methadone programs or other addiction treatment or detoxification programs, and have focused on heroin users. Evaluations of programs in New York City, Massachusetts, Los Angeles, San Francisco, Chicago, Rhode Island, Pittsburgh and Baltimore have been reported in the published literature.[112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123] Because the focus of the evaluations has been on the number of trained individuals and overdose reversals reported, it is not possible to describe the population-level impact of these individual programs. Data from a 2014 survey found that OEND programs in the U.S. had trained and provided naloxone to more than 150,000 individuals between 1996 and 2014, and reported more than 26,000 opioid overdose reversals during this time.[124] Additional evaluations have reported on changes in overdose recognition and response knowledge and/or behaviors as a result of OEND program training.[125, 126, 127, 128, 129, 130] Taken together, these data demonstrate that people at high risk for opioid-related overdose and their friends or family members can successfully be trained to recognize and respond to an overdose and appropriately administer naloxone in an overdose situation.

The literature examining the broader public health impact of naloxone programs is limited. Two identified studies described the Project Lazarus program in North Carolina, which was created in 2008. One component of this program is the co-prescription of naloxone to people at risk for opioid overdose. An initial evaluation of Project Lazarus in Wilkes County, North Carolina, found significant declines in the unintentional drug overdose death rate from a peak of 46.6 deaths per 100,000 population in 2009 to 29.0 deaths per 100,000 in 2010 and 14.4 deaths per 100,000 in 2011.[131, 132] However, because Project Lazarus includes overdose prevention components unrelated to naloxone, it is difficult to determine the exact role naloxone played in the reduction of Wilkes County's unintentional drug overdose deaths.

Walley et al., provide the most robust evaluation examining changes in health outcomes as a result of OEND program implementation. They conducted an interrupted time-series analysis to evaluate the impact of Massachusetts' OEND program on opioid-related overdose deaths and non-fatal opioid overdose-related acute care hospital utilization rates from 2002 to 2009. They found that communities that implemented OEND programs during the study time had statistically significant reductions in opioid-related overdose death rates compared to communities that did not implement OEND programs. Acute care hospital utilizations did not differ between OEND program communities and those that did not implement one.[130]
Based on recent systematic analyses, the available evidence suggests that naloxone is a promising strategy with some evidence of effectiveness in reducing opioid overdose mortality rates.[133] However, the data almost exclusively pertain to reversals of overdoses from heroin and not among people using prescription opioids. Overall the quality of evidence for the impact of naloxone on opioid overdose is low. Limitations of the available studies include lack of randomization of distribution methods; lack of generalizability because the data are almost exclusively based on people who inject drugs, primarily heroin; self-reported outcomes; short-term follow-up; significant loss to follow-up; and lack of control over other events occurring simultaneously that could be responsible for effects.[134]

#5 OVERDOSE EDUCATION AND NALOXONE DISTRIBUTION PROGRAMS

RECOMMENDATIONS FOR ACTION

5.1 ENGAGE WITH THE SCIENTIFIC COMMUNITY TO ASSESS THE RESEARCH NEEDS RELATED TO NALOXONE DISTRIBUTION EVALUATIONS AND IDENTIFY HIGH PRIORITY FUTURE DIRECTIONS FOR NALOXONE-RELATED RESEARCH.

Rationale: Naloxone is a promising strategy for reversing overdose. Rigorous, high quality research is needed to explore the relative effectiveness of naloxone use in different settings, through different OEND mechanisms (including care and follow-up after overdose reversal events), and on prescription opioid (as opposed to heroin) overdose.

Current Status: There are several evaluations currently underway. However, available funding to evaluate the various types of programs being implemented is insufficient. The scientific community needs to further engage in a discussion on the various research approaches to evaluate naloxone programs being implemented in a variety of settings.

5.2 PARTNER WITH PRODUCT DEVELOPERS TO DESIGN NALOXONE FORMULATIONS THAT ARE EASIER TO USE BY NONMEDICAL PERSONNEL AND LESS COSTLY TO DELIVER.

Rationale: As the legal landscape changes to allow broader access to naloxone, different populations may prefer different delivery mechanisms for naloxone. Having multiple products that are easy for nonmedical personnel to use would likely increase uptake and reduce costs. Price is consistently raised as a concern impacting the sustainability of various naloxone distribution programs, and recent reports indicate that the cost of the drug is increasing dramatically.[135]

Current Status: An auto-injector formulation of naloxone (Evzio) was approved by the FDA in April 2014. Several drug manufacturers have submitted applications to the FDA for approval of intranasal naloxone products as well.

5.3 WORK WITH INSURERS AND OTHER THIRD-PARTY PAYERS TO ENSURE COVERAGE OF NALOXONE PRODUCTS.

Rationale: One approach to sustaining expanded access to naloxone is through pharmacy dispensing and coverage through third parties.

Current Status: Some states and localities have made progress in gaining coverage for certain naloxone products. However, this has not been accomplished in a systematic way.

5.4 PARTNER WITH COMMUNITY-BASED OVERDOSE EDUCATION AND NALOXONE DISTRIBUTION PROGRAMS TO IDENTIFY STABLE FUNDING SOURCES TO ENSURE PROGRAM SUSTAINABILITY.

Rationale: Some community-based programs have little to no dedicated funding for the purchase and provision of naloxone. These programs provide critical access to naloxone among high-risk populations.

Current Status: The federal government has identified some grant program funding that can be used to purchase naloxone. However, it is not clear exactly how these funds will impact community-based programs. Other community-based programs have worked with local and state agencies to develop a sustainable funding model and their experience could be informative to other programs across the country.

5.5. ENGAGE WITH THE HEALTHCARE PROFESSIONAL COMMUNITY TO ADVANCE CONSENSUS GUIDELINES ON THE CO-PRESCRIPTION OF NALOXONE WITH PRESCRIPTION OPIOIDS

Rationale: There is no consensus on the patients who should be co-prescribed or prescribed naloxone in general medical settings. Recent studies show a number of logistical and attitudinal barriers to naloxone co-prescription.

Current Status: Several medical societies have adopted resolutions supporting naloxone co-prescription to patients, and some health systems such as the Veterans Administration have begun implementing campaigns to increase naloxone co-prescription. However, there is no consensus on the most appropriate patients for naloxone co-prescription.

STATEMENT OF THE PROBLEM

Opioid addiction can develop from repeated exposure to opioids. Left untreated, opioid addiction commonly results in serious psychosocial problems, medical problems and death from accidental overdose. Since 1997, the number of Americans seeking treatment for addiction to opioid painkillers increased by 900 percent.[136, 137] The sharp increase in the prevalence of opioid addiction has been associated with a parallel increase in opioid-related overdose deaths and with increasing use of heroin.[138] Other health and social problems associated with the epidemic of opioid addiction include rising rates of neonatal abstinence syndrome, HIV and hepatitis C infections;[139] decreased life expectancy in white women; decreased workforce readiness; and decreased availability of parenting in the affected child-raising demographic.

Treatment of opioid addiction is similar to the management of other chronic conditions[140] and involves a bio-psycho-social approach. Unfortunately, the need for opioid addiction treatment is largely unmet.[141] In regions of the country where the epidemic is most severe, there are waiting lists for treatment, especially with buprenorphine. Evidence-based treatment for opioid addiction often involves the use of buprenorphine and methadone, which are currently underutilized. Despite strong evidence supporting the use of buprenorphine and methadone, and evidence that more than 5 million Americans are suffering from opioid addiction, fewer than 1 million are receiving these treatments.[142] A variety of barriers must be removed to allow adequate access to appropriate care.

SYNTHESIS OF AVAILABLE EVIDENCE

Pharmacotherapies for opioid addiction include agonist maintenance with methadone, partial-agonist maintenance with buprenorphine and antagonist treatment with naltrexone. Although some evidence exists supporting use of naltrexone in specific populations,[143] safety and efficacy has not been well established. However, multiple well-designed randomized controlled trials provide strong evidence that buprenorphine maintenance and methadone maintenance are safe, efficacious and cost-effective treatments for opioid addiction.[144] Both buprenorphine and methadone maintenance treatment are associated with reduced overdose risk, reduced risk of HIV infection and improved maternal and fetal outcomes in pregnancy.[145, 146] However, when used short term, especially in detoxification regimens, evidence of enduring benefit is lacking.[147]

Psychosocial approaches to treating opioid addiction include therapeutic communities, cognitive-behavioral therapies and 12-step facilitation, either provided in professional treatment or by mutual support groups (e.g., Narcotics Anonymous). While 12-step programs are valued by many addiction professionals, it has been difficult to determine which elements of these programs may be of greatest therapeutic value. Psychosocial interventions, like medication treatments, may occur in outpatient or inpatient settings. While some studies support improved effectiveness of combining psychosocial therapies with buprenorphine and methadone maintenance, abstinence-based psychosocial approaches that shun medication-assisted treatment are lacking evidence to support the practice.[148, 149]

— The ability to expand access to treatment with methadone is limited by a short supply of licensed programs in non-urban communities and requirements such as daily attendance. Unlike methadone maintenance, buprenorphine can be prescribed in an office-based setting. Unfortunately, there are a variety of barriers to treatment with buprenorphine that include:

— Federal limits on the number of opioid-addicted patients a physician may treat with buprenorphine. A physician is limited to treating up to 30 patients in the first year following receipt of a buprenorphine waiver, after which the physician may apply to treat up to 100 patients.

— Prohibition against nurse practitioners' and physician assistants' prescribing. Nurse practitioners and physicians assistants are ineligible to apply for a buprenorphine waiver, even under the supervision of an addiction specialist.

— Inadequate integration of buprenorphine into primary care treatment. Physicians, nurse practitioners, physicians assistants and other allied health care professionals have little training in the recognition and treatment of opioid addiction.

— Stigma against maintenance treatment for opioid addiction. The misperception that maintenance medications are inappropriate because they substitute one drug for another is a commonly held view. These treatments have suffered from misunderstandings and negative attitudes of the public, patients and providers.[150] Less than half of all licensed addiction treatment programs offer these medications, and less than half of the eligible patients in those programs receive them.[151]

#6 ADDICTION TREATMENT

RECOMMENDATIONS FOR ACTION

6.1 INVEST IN SURVEILLANCE.

Improve epidemiologic surveillance of opioid addiction by revising the National Survey on Drug Use and Health (NSDUH) questions to capture opioid use disorders in patients receiving opioids for the treatment of chronic pain and by identifying other strategies to track the incidence and prevalence of opioid addiction. This effort will involve collaboration with the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Centers for Disease Control and Prevention (CDC).

Rationale: Understanding the size and scope of the opioid addiction problem is essential for developing effective interventions. Revising an existing surveillance tool is a cost effective way to obtain needed information.

Current Status: This effort is not yet underway.

6.2 EXPAND ACCESS TO BUPRENORPHINE TREATMENT.

Addiction specialist physicians are prohibited under federal law from treating more than 100 patients with buprenorphine — a restriction with no counterpart anywhere in medicine and which has led to waiting lists for patients to receive treatment. These federally imposed caps should be lifted. Additional training of prescribers on medication-assisted treatment should be offered and treatment guidelines, such as the American Society of Addiction Medicine (ASAM) Guideline for Medication Assisted Treatment, should be disseminated. Access to buprenorphine treatment across the country should be closely monitored by the federal government. This effort will involve collaboration with SAMHSA and the Drug Enforcement Agency (DEA).

Rationale: Federally imposed caps on the number of patients a physician can treat limit access to buprenorphine.

Current Status: Legislation seeking to lift the buprenorphine patient cap has been introduced in the U.S. Senate. In addition, the Department of Health and Human Services recently announced a plan to lift the cap through the regulatory process.

6.3 REQUIRE FEDERALLY-FUNDED TREATMENT PROGRAMS TO ALLOW PATIENTS ACCESS TO BUPRENORPHINE OR METHADONE

Policies that prevent access to medication-assisted treatment are counter to the evidence and the current standard of care for effective treatment of opioid addiction. This effort will involve collaboration with the SAMHSA, the Centers for Medicare and Medicaid Services and the White House Office of National Drug Control Policy (ONDCP).

Rationale: Buprenorphine is an effective treatment for opioid addition.

Current Status: In 2015, the ONDCP announced that drug court programs will be ineligible to receive future federal funding if they prohibit receipt of buprenorphine and methadone.

6.4 PROVIDE TREATMENT FUNDING FOR COMMUNITIES WITH HIGH RATES OF OPIOID ADDICTION AND LIMITED ACCESS TO TREATMENT.

Advocate for a Targeted Capacity Expansion (TCE) program that will provide federal funding for increased access to buprenorphine and methadone in communities with high rates of opioid addiction and limited access to treatment. This effort will involve collaboration with SAMHSA.

Rationale: Treatment services are disproportionately distributed across communities and do not always reflect need. Using federal resources to identify communities most in need of treatment services and to expand treatment capacity will help to address this disparity.

Current Status: In 2015, SAMHSA issued a request for applications for prescription opioid and heroin addiction TCE programs. SAMSHA identified a total of $11 million in funding to support the program. Additionally, bills have been introduced in Congress that increase funding to states for opioid addiction treatment.

6.5 DEVELOP AND DISSEMINATE A PUBLIC EDUCATION CAMPAIGN ABOUT THE ROLE OF TREATMENT IN ADDRESSING OPIOID ADDICTION.

Utilize information from Health and Human Services (HHS) and the National Institute on Drug Abuse (NIDA) through the CDC and ONDCP to educate providers, patients and their families; health plans; state level law enforcement; and policy makers on the nature of opioid addiction as a chronic brain disease, noting that the strongest evidence supports use of maintenance medication with either methadone or buprenorphine. This campaign should also aim to reduce the stigma associated with effective treatment options. A major public education campaign on appropriate treatment that is comprehensive, evidence-based, and follows best practices in health communication is needed and should be evaluated.

Rationale: There is a lack of awareness about the effectiveness of medication treatment options among providers, patients and their families, health plans, law enforcement, and policy makers, and there is stigma against medication treatment. Both the lack of information and the stigma associated with medication treatment are barriers to greater use of effective treatment. Medication treatment is the standard of care for opioid addiction and it should be known as such among providers and the public at large.

Current Status: Federal health officials from the CDC, National Institues of Health (NIH) and SAMHSA have made public statements supporting medication-assisted treatment. The NIH and SAMHSA have also issued materials for healthcare providers and the public on treatment with buprenorphine. Some health departments, most notably the New York City Department of Health and Mental Hygiene and the Maryland Department of Health and Mental Hygiene, have sponsored efforts to raise awareness and improve access to treatment with buprenorphine and methadone.

6.6 EDUCATE PRESCRIBERS AND PHARMACISTS HOW TO PREVENT, IDENTIFY AND TREAT OPIOID ADDICTION.

Develop, evaluate and disseminate prescriber and pharmacist education to assist in better preventing, identifying and treating opioid addiction. Training should include both information as well as direct skill development in assessment and treatment of opioid addiction. Develop, evaluate and disseminate information about the standard of care for treatment of opioid addiction to substance abuse treatment providers.

Rationale: Prescribers and pharmacists receive little training on substance use disorders. With improved understanding of the etiology of opioid addiction and its treatment, they may be better able to prevent, recognize and care for patients suffering from this condition.

Current Status: The American Society of Addiction Medicine and the American Academy of Addiction Psychiatry are currently involved in efforts to improve medical education about substance use disorders. A coordinated national effort to educate prescribers and pharmacists about opioid addiction is not yet underway.

6.7 SUPPORT TREATMENT-RELATED RESEARCH.

Treatment programs that utilize the most efficacious and cost-effective protocols are needed; research is needed to identify and disseminate such interventions. Specifically, research is needed that answers questions about the relative effectiveness of different types of psychosocial interventions as additions to medication treatment, as well as trials of the enduring effectiveness of psychosocial interventions alone vs. maintenance medication therapies. This effort could include collaboration with the NIH, the Patient-Centered Outcomes Research Institute (PCORI), the Agency for Healthcare Research and Quality (AHRQ), and the CDC.

Rationale: In order to maximize available treatment resources, research about the most effective ways to use medication treatment is needed. In parallel, more effective strategies to implement and disseminate proven efficacious strategies are needed.

Current Status: The NIH is currently funding some research on opioid addiction treatments, including comparisons of treatment interventions.

#7 COMMUNITY-BASED PREVENTION STRATEGIES

STATEMENT OF THE PROBLEM

Prescription drug misuse, abuse and overdose impacts communities across the nation. It is a problem that involves a legal product that is manufactured, marketed and dispensed by professionals through a system that is subject at multiple points to government oversight from different agencies at the federal and state levels. That system has been ineffective in preventing the oversupply of prescription opioids to communities where demand for these products has grown. Whether the supply is in response to demand, a cause of the demand or some combination is unclear. Community engagement in efforts to reduce both the supply of prescription opioids and the demand for them is an under-used, but potentially important part of the solution to the problem. However, there is a dearth of evidence-based community initiatives for addressing prescription drug misuse, abuse and overdose. For the purposes of this report, we consider "communities" to be groups of people defined by a shared experience, such as college students or people living in the same town, or by professional affiliation, such as healthcare providers or pharmacists.

SYNTHESIS OF AVAILABLE EVIDENCE

Defining the problem. Counts of overdose deaths are well publicized and in many ways have defined the concern about prescription opioids as a public health problem. However, additional information about the prevalence of these drugs in communities and homes, and about access to them by nonmedical users through family, friends and underground markets, is needed to better understand opportunities for intervention. Prescription Drug Monitoring Programs (PDMPs) are an important information source. The status of PDMP data, how they are being used, and the potential for greater application of these data are all detailed in Section 3 of this report. However, PDMP data capture information about the initial prescription, and not the dissemination of those drugs beyond the initial recipient. Other studies using cross sectional data provide some insight into the role of family, friends and illegal markets in supplying prescription opioids to people who are abusing, but these data are limited by time and geography. More comprehensive surveillance about prevalence and use is needed.

The supply of prescription opioids is connected to the manufacturing sector that controls production (the amount of product produced), chemistry (e.g., strength, composition, properties) and characteristics (e.g., crush resistance of pills, shelf life) of the drugs produced. Although these supply side issues are being addressed through legislative, regulatory and engineering strategies as discussed in previous sections of this report, an understanding of this supply side context is essential for planning effective community campaigns. The extent to which stakeholders from the supply side are engaged with community prevention advocates and/or involved in community public health campaigns is not known, and needs to be better understood.

Defining solutions. Several professional communities are important stakeholders in the prescription opioid matter. Prescribers, pharmacies and third-party payers are the focus of Sections 1 and 3 included in this document, and we will not duplicate those summaries and recommendations here. We note that those recommendations focus on identifying and intervening with high-risk patient groups who are already using prescription opioids. Here we focus on efforts to engage with patients and the general public about opioid risks and alternatives for pain management prior to the start of misuse or abuse.

Clinical interactions as an opportunity to educate patients about the risks of prescription opioids and alternatives to pain management are not documented in the literature. We are aware of one effort underway at the Johns Hopkins Center for Injury Research and Policy to develop a patient decision aid for emergency room patients who present for pain that would likely lead to an opioid prescription. However, that study is in the field and no results were available at the time of this writing. One community intervention included student nurses as part of a broader community coalition to address prescription drug overdose. The resulting paper focused more on process indicators than on outcome measures, and documents important impacts (e.g., prescription drugs turned in) but did not connect those impacts to overdose or poisoning outcomes. While promising, the intervention lacks the rigorous evaluation required to be considered evidence-based.[152]

Project Lazarus, a community-based initiative in North Carolina, offers perhaps the most insight with regard to population-based impacts on overdose. Included as part of the intervention are a number of strategies to address prescription opioid abuse, misuse and overdose (e.g., naloxone distribution, patient and provider education). Evaluation findings suggest significant declines in overdose deaths and hospital emergency department visits for overdose. [127]

Efforts to raise awareness about the risks associated with prescription opioids and alternatives available for pain management through public education campaigns are underway (e.g., The Medicine Abuse Project aimed at preventing teen misuse/abuse and promoting treatment; Rx for Understanding, a school-based curriculum; the JED Foundation's college campus initiative; and the National Institute on Drug Abuse (NIDA) PEERx program), however, evaluations of such efforts are lacking. Raising

awareness is generally viewed as an important strategy for addressing prescription opioid misuse and offers an opportunity for prevention when combined with other strategies.

Best practices in health promotion suggest that awareness-raising efforts will have maximum impact when combined with other interventions that address the larger context in which the problem is occurring. For this issue, raising awareness could be enhanced with attention to the policy context (e.g., naloxone availability) as well as the need for other services (e.g., addiction treatment) and the supply side. To our knowledge, no community campaigns have engaged the public in efforts to address the supply side of the issue, nor have they engaged supply-side stakeholders to develop comprehensive prevention initiatives.

Primary prevention strategies targeting those who would use these drugs recreationally could adapt existing effective substance abuse prevention programs to the case of opioids. Primary prevention for patients with pain-related conditions will require effective patient education and access to alternative pain management resources (e.g. physical therapy). Assuring that public education initiatives are appropriately targeted, informed by evidence and rigorously evaluated is critically important to assuring that investments are well placed and effective.

Evidence from another problem: Antibiotic overuse. In 1995, the U.S. Centers for Disease Control and Prevention (CDC) launched the National Campaign for Appropriate Antibiotic Use in the Community, which was renamed Get Smart: Know When Antibiotics Work, in 2003. One important aim of the campaign was to decrease the demand for antibiotics by adults and parents of children with viral upper respiratory infections. Multiple studies have demonstrated the campaign's effectiveness, suggesting that improving patient knowledge of risks, benefits and alternatives may be a promising approach to reducing the number of prescriptions. Further studies have investigated the effectiveness of computerized patient education modules promoting awareness of appropriate antibiotic use and provided initial evidence that these interventions can be effective at reducing demand. For community prevention efforts, there are many parallels to the prescription opioid problem — i.e., the drugs are useful in certain circumstances but over-prescribed in many others and patients are generally unaware of the potential individual and societal impacts associated with over-prescribing. Thus, community prevention interventions would do well to draw from the strategies used to reduce antibiotic overuse.

RECOMMENDATIONS FOR ACTION

7.1 INVEST IN SURVEILLANCE TO INFORM HOW PATIENTS IN TREATMENT FOR OPIOID ABUSE AND THOSE WHO HAVE OVERDOSED OBTAIN THEIR SUPPLY. EXISTING SURVEILLANCE EFFORTS SUCH AS THE NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM (NEISS) CAN PROVIDE AN INFRASTRUCTURE TO ACCOMPLISH THIS TASK.

Rationale: Information about the prevalence of prescription opioids in communities and homes, and access to them by nonmedical users through family, friends and underground markets, is needed to better understand opportunities for intervention. Cross-sectional data provide some insight into these questions, but these data are limited. More comprehensive surveillance about prevalence and use is needed.

Current Status: We are unaware of any ongoing surveillance effort to capture information about the source of prescription opioids for people who seek treatment for opioid abuse or overdose.

7.2 CONVENE A STAKEHOLDER MEETING WITH BROAD REPRESENTATION TO CREATE GUIDANCE THAT WILL HELP COMMUNITIES UNDERTAKE COMPREHENSIVE APPROACHES THAT ADDRESS THE SUPPLY OF, AND DEMAND FOR, PRESCRIPTION OPIOIDS IN THEIR LOCALES; IMPLEMENT AND EVALUATE DEMONSTRATION PROJECTS THAT MODEL THESE APPROACHES.

Rationale: Attention to the complex social and political context in which the problem of prescription misuse, abuse and overdose occurs has not been reflected in existing community campaign efforts. Broader stakeholder engagement may yield impactful new approaches.

Current Status: We are unaware of any systematic efforts to utilize community engagement to build comprehensive model programs that address both supply and demand.

7.3 CONVENE AN INTER-AGENCY TASK FORCE TO ASSURE THAT CURRENT AND FUTURE NATIONAL PUBLIC EDUCATION CAMPAIGNS ABOUT PRESCRIPTION OPIOIDS ARE INFORMED BY THE AVAILABLE EVIDENCE AND THAT BEST PRACTICES ARE SHARED.

Rationale: Past success with reducing antibiotic use is generally attributed to a national campaign. Applying lessons learned from that success to the current prescription opioid challenge will increase the likelihood that public education strategies benefit from the available evidence.

Current Status: Public education about the risks of prescription opioids and alternatives for pain management is needed, and many efforts are underway and will likely be developed. The extent to which these efforts are informed by the available evidence is unknown, and there is no central repository for collecting this evidence and sharing best practices.

7.4 PROVIDE CLEAR AND CONSISTENT GUIDANCE ON SAFE STORAGE OF PRESCRIPTION DRUGS.

Rationale: One source of prescription medications for nonmedical users is family and friends. Ensuring prescription medications are not easily accessible may reduce intentional misuse by teens and adults and unintentional misuse by young children.

Current Status: While engineering solutions to packaging hold great promise, as detailed earlier in this report, clear guidance about safe storage options for patients who bring prescription drugs home is needed. Messages should be appropriate for all populations, including those with low literacy and non-English speakers, and should be consistent across all sources — the prescriber, the pharmacist, in the drug packaging materials for patients, and in community campaigns.

7.5 DEVELOP CLEAR AND CONSISTENT GUIDANCE ON SAFE DISPOSAL OF PRESCRIPTION DRUGS; EXPAND ACCESS TO TAKE-BACK PROGRAMS.

Rationale: There is a need for safe disposal options for prescription medications. Guidance from the federal government about how to accomplish safe disposal is needed and can serve to launch community-based take-back initiatives that are responsive to local needs and culture.

Current Status: Clear guidance on how to safely dispose of prescription drugs is lacking; access to take-back programs is also limited and highly variable across jurisdictions. Messages should be appropriate for all populations, including those with low literacy and non-English speakers, and should be consistent across all sources — the prescriber, the pharmacist, in the drug packaging materials for patients, and in community campaigns.

7.6 REQUIRE THAT FEDERAL SUPPORT FOR PRESCRIPTION DRUG MISUSE, ABUSE AND OVERDOSE INTERVENTIONS INCLUDE OUTCOME DATA.

Rationale: Promising interventions are in the field, and have been demonstrated to be feasible and impactful. Population-based outcome data are lacking and needed to inform decisions about replication and scale-up of promising interventions.

Current Status: The federal government is funding a number of interventions to address prescription drug misuse, abuse and overdose. We are unaware of any requirement that outcome data be included with such initiatives.

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COMPLAINT

EXHIBIT #22

Obama Crisis Plan

2011

EPIDEMIC: RESPONDING TO AMERICA'S PRESCRIPTION DRUG ABUSE CRISIS

2011

EXECUTIVE OFFICE OF THE PRESIDENT OF THE UNITED STATES

Background

Prescription drug abuse is the Nation's fastest-growing drug problem. While there has been a marked decrease in the use of some illegal drugs like cocaine, data from the National Survey on Drug Use and Health (NSDUH) show that nearly one-third of people aged 12 and over who used drugs for the first time in 2009 began by using a prescription drug non-medically.[1] The same survey found that over 70 percent of people who abused prescription pain relievers got them from friends or relatives, while approximately 5 percent got them from a drug dealer or from the Internet.[2] Additionally, the latest Monitoring the Future study—the Nation's largest survey of drug use among young people—showed that prescription drugs are the second most-abused category of drugs after marijuana.[3] In our military, illicit drug use increased from 5 percent to 12 percent among active duty service members over a three-year period from 2005 to 2008, primarily attributed to prescription drug abuse.[4]

Although a number of classes of prescription drugs are currently being abused, this action plan primarily focuses on the growing and often deadly problem of prescription opioid abuse. The number of prescriptions filled for opioid pain relievers—some of the most powerful medications available—has increased dramatically in recent years. From 1997 to 2007, the milligram per person use of prescription opioids in the U.S. increased from 74 milligrams to 369 milligrams, an increase of 402 percent.[5] In addition, in 2000, retail pharmacies dispensed 174 million prescriptions for opioids; by 2009, 257 million prescriptions were dispensed, an increase of 48 percent.[6] Further, opiate overdoses, once almost always due to heroin use, are now increasingly due to abuse of prescription painkillers.[7]

These data offer a compelling description of the extent to which the prescription drug abuse problem in America has grown over the last decade, and should serve to highlight the critical role parents, patients, healthcare providers, and manufacturers play in preventing prescription drug abuse.

These realities demand action, but any policy response must be approached thoughtfully, while acknowledging budgetary constraints at the state and Federal levels. The potent medications science has developed have great potential for relieving suffering, as well as great potential for abuse. There are many examples: acute medical pain treatment and humane hospice care for cancer patients would be impossible without prescription opioids; benzodiazepines are the bridge for many people with serious anxiety disorders to begin the process of overcoming their fears; and stimulants have a range of valuable uses across medical fields. Accordingly, any policy in this area must strike a balance between our desire

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to minimize abuse of prescription drugs and the need to ensure access for their legitimate use. Further, expanding effective drug abuse treatment is critical to reducing prescription drug abuse, as only a small fraction of drug users are currently undergoing treatment.

This Prescription Drug Abuse Prevention Plan expands upon the Administration's *National Drug Control Strategy* and includes action in four major areas to reduce prescription drug abuse: education, monitoring, proper disposal, and enforcement. First, education is critical for the public and for healthcare providers to increase awareness about the dangers of prescription drug abuse, and about ways to appropriately dispense, store, and dispose of controlled substance medications. Second, enhancement and increased utilization of prescription drug monitoring programs will help to identify "doctor shoppers" and detect therapeutic duplication and drug-drug interactions. Third, the development of consumer-friendly and environmentally-responsible prescription drug disposal programs may help to limit the diversion of drugs, as most non-medical users appear to be getting the drugs from family and friends. Fourth, it is important to provide law enforcement agencies with support and the tools they need to expand their efforts to shut down "pill mills" and to stop "doctor shoppers" who contribute to prescription drug trafficking.

I. Education

A crucial first step in tackling the problem of prescription drug abuse is to raise awareness through the education of parents, youth, patients, and healthcare providers. Although there have been great strides in raising awareness about the dangers of using illegal drugs, many people are still not aware that the misuse or abuse of prescription drugs can be as dangerous as the use of illegal drugs, leading to addiction and even death.

Parents and youth in particular need to be better educated about the dangers of the misuse and abuse of prescription drugs. There is a common misperception among many parents and youth that prescription drugs are less dangerous when abused than illegal drugs because they are FDA-approved. Many well-meaning parents do not understand the risks associated with giving prescribed medication to a teenager or another family member for whom the medication was not prescribed. Many parents are also not aware that youth are abusing prescription drugs; thus, they frequently leave unused prescription drugs in open medicine cabinets while making sure to lock their liquor cabinets. These misperceptions, coupled with increased direct-to-consumer advertising, which may also contribute to increased demand for medications,[8,9] makes effective educational programs even more vital to combating prescription drug abuse.

In addition, prescribers and dispensers, including physicians, physicians assistants, nurse practitioners, pharmacists, nurses, prescribing psychologists, and dentists, all have a role to play in reducing prescription drug misuse and abuse. Most receive little training on the importance of appropriate prescribing and dispensing of opioids to prevent adverse effects, diversion, and addiction. Outside of specialty addiction treatment programs, most healthcare providers have received minimal training in how to

8. Frosch DL, Grande D, Tarn DM, Kravitz RL. A decade of controversy: balancing policy with evidence in the regulation of prescription drug advertising. *Am J Public Health*. 2010;100(1):24-32.

9. Greene JA, Kesselheim AS. Pharmaceutical marketing and the new social media. *N Engl J Med*. 2010;363(22):2087-2089.

recognize substance abuse in their patients. Most medical, dental, pharmacy, and other health professional schools do not provide in-depth training on substance abuse; often, substance abuse education is limited to classroom or clinical electives. Moreover, students in these schools may only receive limited training on treating pain.

A national survey of medical residency programs in 2000 found that, of the programs studied, only 56 percent required substance use disorder training, and the number of curricular hours in the required programs varied between 3 to 12 hours.[10] A 2008 follow-up survey found that some progress has been made to improve medical school, residency, and post-residency substance abuse education; however, these efforts have not been uniformly applied in all residency programs or medical schools.[11]

Educating prescribers on substance abuse is critically important, because even brief interventions by primary care providers have proven effective in reducing or eliminating substance abuse in people who abuse drugs but are not yet addicted to them. In addition, educating healthcare providers about prescription drug abuse will promote awareness of this growing problem among prescribers so they will not over-prescribe the medication necessary to treat minor conditions. This, in turn, will reduce the amount of unused medication sitting in medicine cabinets in homes across the country.

The following action items will be taken to improve educational efforts and to increase research and development:

Healthcare Provider Education:

- Work with Congress to amend Federal law to require practitioners (such as physicians, dentists, and others authorized to prescribe) who request DEA registration to prescribe controlled substances to be trained on responsible opioid prescribing practices as a precondition of registration. This training would include assessing and addressing signs of abuse and/or dependence. (**ONDCP/FDA**/DEA/SAMHSA)
- Require drug manufacturers, through the Opioid Risk Evaluation and Mitigation Strategy (REMS), to develop effective educational materials and initiatives to train practitioners on the appropriate use of opioid pain relievers. (**FDA**/ONDCP/SAMHSA)
- Federal agencies that support their own healthcare systems will increase continuing education for their practitioners and other healthcare providers on proper prescribing and disposal of prescription drugs. (**VA**/HHS/**IHS/DOD/BOP**)
- Work with appropriate medical and healthcare boards to encourage them to require education curricula in health professional schools (medical, nursing, pharmacy, and dental) and continuing education programs to include instruction on the safe and appropriate use of opioids to treat pain while minimizing the risk of addiction and substance abuse. Additionally, work with relevant medical, nursing, dental, and pharmacy student groups to help disseminate educational materials, and establish student programs that can give community educational presentations

10. Isaacson JH, Fleming M, Kraus M, Kahn R, Mundt M. A National Survey of Training in Substance Use Disorders in Residency Programs. *J Stud Alcohol*. 61(6):912-915. 2000.
11. Polydorou S, Gunderson EW, Levin FR. Training Physicians to Treat Substance Use Disorders. *Curr Psychiatry Rep*. 10(5):399-404. 2008.

on prescription drug abuse and substance abuse. (HHS/**SAMHSA**/**ONDCP**/FDA/HRSA/NIDA/DOD/VA)

- In consultation with medical specialty organizations, develop methods of assessing the adequacy and effectiveness of pain treatment in patients and in patient populations, to better inform the appropriate use of opioid pain medications. (HHS/**CDC**/**SAMHSA**/FDA)
- Work with the American College of Emergency Physicians to develop evidence-based clinical guidelines that establish best practices for opioid prescribing in the Emergency Department. (**CDC**/FDA/ONDCP/NIDA/SAMHSA/CMS)
- Work with all stakeholders to develop tools to facilitate appropriate opioid prescribing, including development of Patient-Provider Agreements and guidelines. (HHS/**FDA**/SAMHSA/NIDA)

Parent, Youth, and Patient Education:

- Enlist all stakeholders to support and promote an evidence-based public education campaign on the appropriate use, secure storage, and disposal of prescription drugs, especially controlled substances. Engage local anti-drug coalitions, and other organizations (chain pharmacies, community pharmacies, boards of pharmacies, boards of medicine) to promote and disseminate public education materials and to increase awareness of prescription drug misuse and abuse. (**ONDCP**/CDC/FDA/DEA/IHS/ED/SAMHSA/DOD/VA/EPA)
- Require manufacturers, through the Opioid Risk Evaluation and Mitigation Strategy (REMS), to develop effective educational materials for patients on the appropriate use and disposal of opioid pain relievers. (**FDA**/ONDCP/SAMHSA)
- Working with private-sector groups, develop an evidence-based media campaign on prescription drug abuse, targeted to parents, in an effort to educate them about the risks associated with prescription drug abuse and the importance of secure storage and proper disposal of prescription drugs (including through public alerts or other approaches to capture the attention of busy parents). (**ONDCP**/ONC)

Research and Development:

- Expedite research, through grants, partnerships with academic institutions, and priority New Drug Application review by FDA, on the development of treatments for pain with no abuse potential as well as on the development of abuse-deterrent formulations (ADF) of opioid medications and other drugs with abuse potential. (**NIDA**/**FDA**)
- Continue advancing the design and evaluation of epidemiological studies to address changing patterns of abuse. (**CDC**/FDA/NIDA)
- Provide guidance to the pharmaceutical industry on the development of abuse-deterrent drug formulations and on post-market assessment of their performance. (**FDA**)

II. Tracking and Monitoring

Forty-three states have authorized prescription drug monitoring programs (PDMPs). PDMPs aim to detect and prevent the diversion and abuse of prescription drugs at the retail level, where no other automated information collection system exists, and to allow for the collection and analysis of prescription data more efficiently than states without such a program can accomplish. However, only thirty-five states have operational PDMPs. These programs are established by state legislation and are paid for by a combination of state and Federal funds. PDMPs track controlled substances prescribed by authorized practitioners and dispensed by pharmacies. PDMPs can and should serve a multitude of functions, including: assisting in patient care, providing early warning of drug abuse epidemics (especially when combined with other data), evaluating interventions, and investigating drug diversion and insurance fraud.[12]

In 2002, a General Accounting Office report concluded that state PDMPs provide a useful tool to reduce drug diversion, based largely on the opinion of PDMP managers and law enforcement agencies.[13] Three ecologic studies have since examined PDMP effects on overall state rates. An analysis in 2006 found that PDMPs were associated with lower rates of substance abuse treatment admission.[14] A later study used poison control center contacts and abuse/misuse exposures in states with and without PDMPs to evaluate how PDMPs affected abuse/misuse rates for long-acting opioids versus immediate release opioids. The study found that PDMPs were associated with slower rates of increase in abuse/misuse over time.[15] Most recently, a study found no association between having a PDMP and lower rates of overdose mortality, although the study was evaluating PDMPs between 1999 and 2005.[16] One additional study has examined the effect of a trial of using PDMP data in an emergency department. It found that PDMP data changed clinical management in 41 percent of cases. Of these, 61 percent received fewer or no opioid pain medications than had been originally planned by the physician prior to reviewing the PDMP data, and 39 percent received more opioid medication than previously planned because the physician was able to confirm the patient didn't have a recent history of opioid use.[17] In summary, PDMPs appear to be a promising approach, but more work is needed to determine how to maximize their effectiveness.

Reducing prescription drug abuse requires a combination of Federal, state, and local action. All involved need to be informed on how to use available data sets to identify areas on which to concentrate their efforts. For example, in Massachusetts, the PMP Center of Excellence at Brandeis University developed geospatial mapping of PDMP data, combined with data on prescription drug overdose ED visits and

12. PDMP data cannot be used as evidence in court.

13. GAO Report to the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives. Prescription Drugs: State Monitoring Programs Provide Useful Tool to Reduce Diversion. May 2002. http://www.gao.gov/new.items/d02634.pdf.

14. Simeone R, Holland L. An Evaluation of Prescription Drug Monitoring Programs. 2006. Available from URL: http://www.simeoneassociates.com/simeone3.pdf.

15. Reifler L, Droz D, Bartelson BB, Bailey E, Schnoll S, Dart RC. RADARS® system poison center opioid abuse and misuse rates over time in states with and without active prescription monitoring programs. Poster presented at: American Public Health Association Conference; 2010 Nov 6–10, Denver, CO.

16. Paulozzi LJ, Kilbourne EM, Desai HA. Prescription drug monitoring programs and death rates from drug overdose. Pain Med 2011. doi: 10.1111/j.1526-4637.2011.01062.x. [Epub ahead of print]

17. Baehren DF, Marco, CA, Droz DE, et al. A Statewide Prescription Monitoring Program Affects Emergency Department Prescribing Behaviors. *Annals of Emergency Medicine*. 56(1):19-23. 2010.

prescription drug overdose deaths, to identify concentrations in three suburban areas of the state. Coordination of efforts like this enables maximization of limited resources.

A major effort must be undertaken to improve the functioning of state PDMPs, especially regarding real-time data access by clinicians, and to increase inter-state operability and communication. Furthermore, we must identify stable financial support to maximize the utility of PDMPs, which will help reduce prescription drug diversion and provide better healthcare delivery.

To further these goals, the following actions will be taken:

- Work with states to establish effective PDMPs in every state, including leveraging state electronic health information exchange activities, and to require prescribers and dispensers to be trained in their appropriate use. Encourage research on PDMPs to determine current effectiveness and identify ways to improve effectiveness. (**ONDCP**/SAMHSA/DOJ/NIJ/NIDA/CDC/ONC)
- Support the National All Schedules Prescription Electronic Reporting (NASPER) Act reauthorization in Congress. NASPER is a formula grant program administered by the Substance Abuse and Mental Health Services Administration (SAMHSA) that funds state PDMPs. The program outlines specific, uniform criteria states must have in place to be awarded funding, which increases consistency among state PDMPs. (**SAMHSA**/ONDCP)
- Work with Congress to pass legislation to authorize the Secretary of Veterans Affairs (VA) and the Secretary of Defense (DOD) to share patient information on controlled substance prescriptions with state PDMPs. (**VA/DOD/ONDCP**)
- Encourage federally funded healthcare programs such as IHS and DOD and VA (when authorized to do so) to provide controlled substance prescription information electronically to the PDMPs in states in which they operate healthcare facilities or pharmacies. In addition, DOD, VA, and IHS are encouraged to evaluate the practice of having prescribers check PDMPs for patient controlled substance prescription histories before generating prescriptions for controlled substances. (**DOD/HHS/IHS/VA**)
- Explore the feasibility of providing reimbursement to prescribers who check PDMPs before writing controlled substance prescriptions for patients covered under insurance plans. (**ONDCP**)
- Evaluate existing programs that require doctor shoppers and people abusing prescription drugs to use only one doctor and one pharmacy. The PMP Center of Excellence at Brandeis University will convene a meeting in 2011 with private insurance payers to begin discussions on these topics. (**ONDCP**/DOJ/HHS/SAMHSA)
- Work with HHS and CMS to evaluate the utility of state PDMPs for reducing Medicare and Medicaid fraud, as suggested in the 2009 GAO report—Medicaid: Fraud and Abuse Related to Controlled Substances Identified in Selected States. (**HHS/CMS**/DEA/ONDCP)
- Issue the Final Rule on DEA Electronic Prescribing of Controlled Substances. (**DEA**/ONC/CMS)
- Increase the use of Screening, Brief Intervention, and Referral to Treatment (SBIRT) programs to help healthcare providers identify and prevent prescription drug abuse problems in primary healthcare settings by working with healthcare providers to increase awareness and training

for these programs, and incorporating the use of Health Information Technologies (HIT) such as Electronic Health Records to enhance SBIRT programs. (HHS/**SAMHSA**/HRSA/**CMS**/ONC)

- Identify ways in which Health Information Technologies (HIT) such as Electronic Health Records can improve prescription drug abuse information. (**ONC**/CMS/SAMHSA).
- Test the usefulness of CDC's real-time BioSense surveillance system for generating timely, population-based measures of prescription drug abuse in selected communities. In addition, use information from the NIDA Community Epidemiology Workgroup to monitor and detect locations where increased abuse is occurring to help target limited resources. (HHS/**CDC**/ONDCP/SAMHSA/FDA/NIDA)
- Assess the usefulness of the Drug Abuse Warning Network (DAWN) and how it can best be used for community epidemiology. (HHS/**SAMHSA**/CDC)
- Expand upon DOJ's pilot efforts to build PDMP interoperability across state lines, including leveraging state electronic health information exchange activities. Work to expand interstate data sharing among PDMPs through the Prescription Drug Information Exchange (PMIX). (**DOJ**/**BJA**/DEA/HHS/SAMHSA/ONC)
- Evaluate current databases that measure the extent of prescription drug use, misuse, and toxicity, clinical use of safe opioid prescribing practices, and access to high-quality pain management services, focusing on improving these databases and identifying new sources of data (HHS/ONDCP/CDC)

III. Proper Medication Disposal

Prescription drug abuse is a significant public health and public safety issue, and a large source of the problem is a direct result of what is in Americans' medicine cabinets. SAMHSA's 2009 National Survey on Drug Use and Health found that over 70 percent of people who used prescription pain relievers non-medically got them from friends or relatives, while approximately 5 percent got them from a drug dealer or from the Internet. The same survey showed the scale of the problem is vast with more than 7 million Americans reporting use of a prescription medication for non-medical purposes in the past 30 days.[18] Therefore, a comprehensive plan to address prescription drug abuse must include proper disposal of unused, unneeded, or expired medications. Providing individuals with a secure and convenient way to dispose of medications will help prevent diversion and abuse, and help to reduce the introduction of drugs into the environment.

In order to protect human health and the environment, it is vital that collected prescription drugs be appropriately disposed of in an environmentally safe manner. Thus, prescription drugs collected from individuals are to be disposed of in accordance with Federal, state, and local laws and regulations. Until prescription drug disposal programs are available to all communities, an important environmental safety message in the fight against improper medication disposal is to recommend against flushing prescription drugs with the few exceptions noted by the Food and Drug Administration (FDA). Instead

18. *Results from the 2009 National Survey on Drug Use and Health (NSDUH): National Findings*, SAMHSA (2010). http://oas.samhsa.gov/NSDUH/2k9NSDUH/2k9ResultsP.pdf.

of flushing, prescription drugs should be disposed of in sealed plastic bags with filler such as coffee grounds or kitty litter. However, due to public health concerns, the FDA does recommend disposal via flushing for certain opioid pain relievers that can pose life-threatening risks from accidental ingestion.

The following actions will be taken to increase proper disposal of prescription drugs and prevent diversion:

- While the administrative process to establish the DEA medication disposal rule is underway,[19] DEA and other Federal agencies shall conduct additional take-back activities. Information about the take-back events shall be distributed to local anti-drug coalitions, HIDTAs, and other organizations (chain pharmacies, boards of pharmacies, boards of medicine, environmental agencies, etc). (**DEA**/ONDCP)
- Once DEA regulations on controlled substance prescription drug disposal have been established, develop and execute a robust public education initiative to increase public awareness and provide education on new methods of safe and effective drug return and disposal. (**ONDCP**/EPA/DEA/FDA/CDC/HHS/SAMHSA/NIDA)
- Once DEA regulations have been established, engage PhRMA and others in the private sector to support community-based medication disposal programs. (**ONDCP**/FDA/DEA/HHS/CDC/SAMHSA/EPA)

IV. Enforcement

Along with the increased legitimate use of prescription opioid medications in healthcare settings, there is also a small group of practitioners who abuse their prescribing privileges by prescribing these medications outside the usual course of professional practice or for illegitimate purposes. This has, in some areas, resulted in practitioners illegally prescribing and/or dispensing prescription controlled substances and other prescription drugs under the banner of medical care. These providers and clinics not only endanger the individuals receiving these medications, but also pose serious threats to the communities where they are located.

In addition, a number of "patient"-centered abuses have evolved, most notably "doctor shopping." Doctor shoppers visit multiple prescribers, in different locations within and outside of their states of residence, in order to receive controlled substances and other prescription drugs for diversion and/or abuse. These community-based problems require community-based solutions.

The following actions will be taken to assist states to address doctor shopping and pill mills:

- ONDCP, the National Methamphetamine and Pharmaceutical Initiative (NMPI), a law enforcement training initiative funded by HIDTA, and DEA will contribute to the curriculum for the pharmaceutical crime investigation and prosecution training program sponsored by BJA in 2011. Target training to states with the highest need. (**ONDCP**/DOJ/DEA/HIDTA)

19. The DEA rule-making process is expected to take 12 to 24 months. Before final regulations can be implemented DEA must issue a Notice of Proposed Rule-Making and then consider public comments submitted on the Proposed Rule. Once this has occurred, DEA can issue a Final Rule.

- Increase training to law enforcement and prosecutor groups at national and regional conferences. (**ONDCP**/DEA)
- Continue aggressive enforcement actions against pain clinics and prescribers who are not prescribing within the usual course of practice and not for legitimate medical purposes. (DOJ/**DEA**, HHS, State Medical Boards)
- Work with the appropriate groups to write and disseminate a Model Pain Clinic Regulation Law taking into consideration: 1) registration of these facilities with a state entity; 2) guidance for rules regarding number of employees, location, hours of operation; 3) penalties for operating, owning, or managing a non-registered pain clinic; 4) requirements for counterfeit-resistant prescription pads and reports of theft/loss of such pads; 5) disciplinary procedures to enforce the regulations; and 6) a procedure to allow patient records to be reviewed during regular state inspections. (**ONDCP**)
- Increase HIDTA intelligence-gathering and investigation of prescription drug trafficking, and increase joint investigations by Federal, state, and local agencies. (**ONDCP**/HIDTA/DOJ/DEA)
- Identify and seek to remove administrative and regulatory barriers to "pill mill" and prescriber investigations that impair investigations while not serving another public policy goal. (**ONDCP**/DOJ/**DEA**/HHS/FDA)
- Expand the use of PDMP data to identify criminal prescribers and clinics by the volume of selected drugs prescribed. Encourage best practices for PDMPs, such as PDMP reporting of such prescribers and clinics to pharmacies, law enforcement, and insurance providers. (DOJ/**DEA**)
- Use PDMP data to identify "doctor shoppers" by their numbers of prescribers or pharmacies. Encourage best practices such as identifying such individuals to their prescribers and pharmacies, law enforcement and insurance providers. (DOJ/**BJA**)

V. Prescription Drug Abuse Plan Goals

National Drug Control Strategy Five Year Goal for Prescription Drug Abuse

- 15 percent reduction in non-medical use of prescription-type psychotherapeutic drugs in the past year among people 12 years of age and older.

Prescription Drug Abuse Prevention Plan Goals

- Have an approved and implemented Risk Evaluation and Mitigation Strategy for certain long-acting and extended release opioids within 12 months;
- Write and disseminate a Model Pain Clinic Regulation Law within 12 months;
- Engage and work with Federal agencies and stakeholders to develop and implement a national public education campaign on prescription drug abuse and safe and proper medication disposal within 24 months;

- IHS will increase the number of collaborative practice agreements that involve pharmacists prescribing privileges and monitoring of pain medication prescribing within 18 months;
- Complete rule-making and implement regulations for medication disposal within 24 months;
- Have legislation passed that requires prescribers applying for DEA registration to complete training on the appropriate and safe use, and proper storage and disposal of schedule II and III opioids. Legislation to be passed within 24 months;
- FDA intends to issue a guidance document on developing abuse deterrent drug formulations and on post-market assessment of their performance within 24 months;
- Have DOD, VA, and IHS provide controlled substance prescription information electronically to PDMPs in states in which they operate healthcare facilities and pharmacies within 24 months;
- Increase by 25 percent the number of states reimbursing for SBIRT within 24 months;
- Increase by 25 percent the number of HIDTAs involved in intelligence gathering and investigation around prescription drug trafficking and participation on statewide and regional prescription drug task forces within 24 months;
- Have legislation in all 50 states establishing Prescription Drug Monitoring Programs within 36 months;
- Expand by 10 percent, within 36 months, the available funding for treatment to increase access since only a small fraction of drug users currently undergo treatment;
- Decrease by 15 percent the number of unintentional overdose deaths related to opioids within 60 months.

Summary and Call to Action

Research and medicine have provided a vast array of medications to cure disease, ease suffering and pain, improve the quality of life, and save lives. This is no more evident than in the field of pain management. However, as with many new scientific discoveries and new uses for existing compounds, the potential for diversion, abuse, morbidity, and mortality are significant. Prescription drug misuse and abuse is a major public health and public safety crisis. As a Nation, we must take urgent action to ensure the appropriate balance between the benefits these medications offer in improving lives and the risks they pose. No one agency, system, or profession is solely responsible for this undertaking. We must address this issue as partners in public health and public safety. Therefore, ONDCP will convene a Federal Council on Prescription Drug Abuse, comprised of Federal agencies, to coordinate implementation of this prescription drug abuse prevention plan and will engage private parties as necessary to reach the goals established by the plan.[20]

20. Accomplishment of the plan and its goals is dependent on the availability of resources.